Supplemental Material

New Genetic variants for Cardiac Structure and Function –

The EchoGen Consortium

Conflicts of interest

The authors of this manuscript declare to have the following potential conflicts of interest according to JCI's policy:

Ownership: GFM: owner of Cardiovascular Engineering, Inc., a company that develops and manufactures devices to measure vascular stiffness;

Income: EI: advisor and consultant for Precision Wellness, Inc., and advisor for Cellink for work unrelated to the present project; GFM: consultant to and receives honoraria from Novartis, Merck, Servier and Philips; PSW: honoraria for lectures or consulting from Boehringer Ingelheim, Bayer Health Care, AstraZeneca, Sanofi-Aventis and Public Health, Heinrich-Heine-University Düsseldorf. SB: honoraria for lectures from Abbott, Abbott Diagnostics, Astra Zeneca, Bayer, Boehringer Ingelheim, Medtronic, Pfizer, Roche, SIEMENS Diagnostics, SIEMENS, Thermo Fisher and member of Advisory Boards and consultant for Boehringer Ingelheim, Bayer, Novartis, Roche and Thermo Fisher. SJS: consulting fees from Bayer, Novartis, and Sanofi.,

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Online Methods and Supplemental Material:

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1 ONLINE METHODS

1.1 Echocardiographic Methods

1.1.1 Harmonization and quality issues

An important issue for meta-analysis of data from different cohorts is the compliance with high quality phenotyping standards. Echocardiographic data used for these analyzes were recorded for research but not taken from clinical routine. For echocardiography potential sources of variability have been identified and described previously[1], including inter- and intra-reader and sonographer variability, within subject variability, temporal drift within laboratories, and biases due to missing data[2,3]. Methods that have previously demonstrated to enhance echo reproducibility have been applied by the participating cohorts of the EchoGen consortium at each study site, standardized equipment and imaging and reading protocols, trained sonographers and readers who periodically undergo reading review sessions, averaging multiple measurements, substituting 2D measurements when M-mode measurements are unreliable, assessment of intra-reader and inter-reader agreement, and analyses of temporal drifts[1,3-6].

1.1.2 Echo examinations, parameters and definitions

Transthoracic echocardiography was performed in each cohort by trained technicians or physicians. All measurements were performed according to the current American and European guidelines for the echocardiographic assessment of the left ventricle[7]. For the present investigation we analyzed 5 LV structural, 2 systolic functional, and 7 diastolic functional parameters, as well as 2 binary diastolic traits.

- **LV structural parameters:**

  Two-dimensional guided M-mode measurements of the parasternal long axis view of the LV and aortic root were obtained:

  - ***LV diastolic internal dimension (LVDD)***
  - ***LV wall thickness (LVWT)***, calculated as the sum of posterior wall and interventricular septum measurements
  - ***LV mass (LVM)***, calculated by using the formula 0.8 [1.04{(LV diastolic internal dimension + interventricular septum + posterior wall)^3 −(LV diastolic internal dimension)^3}] + 0.6 [7,8]
  - ***Left atrial antero-posterior diameter (LA)***
  - ***Aortic root diameter (AoD)*** *, diameter of the aortic root (at the maximal diameter of the sinuses of Valsalva), obtained from the parasternal long-axis view*[7]
  - **LV systolic function parameters:**

  Also from the parasternal long axis view the following variables were obtained:

  - ***Left ventricular fractional shortening (FS)***, a quantitative measure of LV systolic function, calculated using the formula ([LV end diastolic dimension – LV end systolic dimension]/ LV end diastolic dimension x 100)
  - ***LV systolic dysfunction (LVSD)***, defined as the presence of reduced fractional shortening (<29%, which corresponds to an ejection fraction of 50%) on M-mode or a diminished ejection fraction (<50%) on 2-dimensional echocardiography [9]. If a cohort only had categorical data on systolic dysfunction available, for example a categorical visual estimate of LV function, these were recoded into a binary variable best representing the cut-offs above.

- **LV diastolic functional parameters:**

For the analyses of all LV diastolic functional parameters only subjects with a preserved LV ejection fraction (EF) were considered, defined according one of the following methods (method 1 preferred): 1. EF (modified Simpson method) ≥ 50%; 2. EF (Teichholz method) ≥ 50%; 3. Fractional shortening ≥ 29%; 4. Visual estimation of EF as fair or poor. Further details about the application of the different methods by cohorts is given in **Supplemental Material Online, *Table S 3***.

From the apical 4-chamber view the following variables were obtained by Doppler imaging of the mitral inflow:

- ***Peak velocity of the mitral E-wave (Mv-E)***
- ***Peak velocity of the mitral A-wave (Mv-A)***
- ***Ratio of the peak velocity of the mitral E-Wave divided by the peak velocity of the mitral A-wave***. This ration was determined during breathing baseline in all cohorts ***(E/A)*** and during Valsalva maneuver in some cohorts ***(E/A_val)***.
- ***Deceleration time of the mitral E-wave (DecTime)***

In addition, a pulse-wave Doppler imaging was obtained from the apical 5-chamber or long-axis view and the sample volume placed within the LVOT, but in proximity to the anterior mitral valve leaflet to record both inflow and outflow signals and measure the following parameter:

- ***Isovolumetric relaxation time (IVRT)***, an additional index of diastolic function, defined as the interval from the closure of the aortic valve to the opening of the mitral valve.

Moreover, tissue Doppler imaging (TDI) was applied in some cohorts to obtain the following diastolic parameters:

- ***Peak velocity of the excursion of the lateral mitral annulus in the early diastolic phase (E´)***
- ***Ratio of the peak velocity of the excursion of the lateral mitral annulus in the early diastolic phase by TDI and the peak velocity of the mitral E-wave by Doppler imaging (E/E´)***

Alternative to TDI Doppler imaging of the pulmonary venous inflow was used in some cohorts to achieve these parameters: systolic pulmonary venous forward flow (S), diastolic pulmonary venous forward flow (D), and ratio of systolic and diastolic pulmonary venous flow (S/D).

- **Binary diastolic LV traits:**

For the definition of these variables the classification of diastolic function by *Redfield et al.* was applied[10]. Measurement of diastolic function was based on Doppler imaging of the mitral inflow and either TDI of the mitral annulus or Doppler imaging of the pulmonary venous inflow in combination with E/A_val measured by Doppler imaging of the mitral inflow.

The following binary diastolic traits were calculated:

- ***Diastolic Dysfunction with preserved ejection fraction (DDpEF)*:** Cases were defined by an EF ≥ 50%, no symptoms of heart failure, no medicated

heart failure AND evidence for mild, moderate or severe LV diastolic dysfunction. Controls were defined by an EF ≥ 50%, no symptoms of heart failure, no medicated heart failure AND a normal LV diastolic function.

- ***Heart Failure with preserved ejection fraction – definition (HFpEF)*****:** Cases were defined by an EF ≥ 50%, symptoms of heart failure (NYHA class ≥ 2) AND/OR medicated heart failure AND evidence for mild, moderate or severe LV diastolic dysfunction. Controls were asymptomatic individuals with preserved systolic and diastolic LV function defined as an EF ≥ 50%, no symptoms of heart failure, no medicated heart failure AND normal LV diastolic function.

Participants with valvular disease were excluded from the analyses of left ventricular dimensions and systolic function, if this information was known or recorded during the echocardiographic examination. Detailed echocardiographic methods used and distributions of traits in each cohort study are reported in the **Supplemental material, *Tables S3 and S4***.

1.2 Methods used for look-up in other cohorts

AortaGen

To determine whether SNPs that were associated with aortic diameter were also associated with aortic stiffness, as assessed by carotid-femoral pulse wave velocity, we evaluated the top SNP from each of the 7 novel aortic diameter loci. Lookups were derived from a previously published meta-analysis of genome wide association results for carotid-femoral pulse wave velocity from 9 cohorts that included 20,634

participants[11]. After accounting for 7 tests, the adjusted threshold for significance was set at a *P* values < 0.007.

CHARGE-HF

The association of the two novel SNPs for left ventricular diastolic diameter with incident heart failure was assessed using the summary statistics of the meta-analysis of four population-based cohorts of adults of European ancestry (Cardiovascular Health Study, Framingham Heart Study, Atherosclerosis Risk In Communities Study and Rotterdam Study) including a total of 20,926 participants free of diagnosed heart failure at baseline, in whom 2,526 cases of incident heart failure occurred during a mean follow-up of 11.5 years[12]. There is partial overlap between the samples of the Cardiovascular Health Study, the Framingham Heart Study and the Rotterdam Study included in CHARGE-HF and in the present study.

Generation R Study

The Generation R Study is a population-based, prospective cohort study from fetal life onwards, including pregnant women with an expected delivery date between April 2002 and January 2006, living in the city of Rotterdam, the Netherlands. A detailed description of the design of study has been published previously[12]. DNA was extracted from cord blood, or, if cord blood was unavailable, from blood samples taken at the 6-year visit, according to a standardized protocol.

Information on SNPs used in the present analysis was extracted from the GWAs database, details of which are described in the supplemental material of this paper. Analyses were restricted to singleton, live born children of European ethnic origin without congenital heart or kidney malformations, in whom echocardiography was

performed during the follow-up at age 6. Analyses were adjusted for age, sex, height, weight and the first four principal components based on the GWAs data.

LURIC

The Ludwigshafen Risk and Cardiovascular Health (LURIC) study is an ongoing prospective study of more than 3,300 individuals of German ancestry in whom cardiovascular and metabolic phenotypes (CAD, MI, dyslipidemia, hypertension, metabolic syndrome and diabetes mellitus) have been defined or ruled out using standardized methodologies in all study participants. Inclusion criteria for LURIC were: German ancestry (limitation of genetic heterogeneity), clinical stability (except for acute coronary syndromes) and availability of a coronary angiogram. Exclusion criteria were: any acute illness other than acute coronary syndromes, any chronic disease where non-cardiac disease predominated and a history of malignancy within the last five years. A 10-year clinical follow-up for total and cause specific mortality has been completed. Participants were genotyped using the Affymetrix 6.0 array and datasets were imputed to the HapMap2 and 1000G reference panels. Association of SNPs with all-cause mortality, cardiovascular mortality and death due to heart failure was analyzed using the Cox proportional hazards model.

CARDIOGRAMPLUSC4D

The associations of the novel SNPs with myocardial infarction and coronary artery disease were looked up in the publicly available dataset of the CARDIOGRAMplusC4D Consortium, including more than 180,000 individuals of which 60,000 are cases of coronary artery diasease and myocardial infarction [downloaded from www.CARDIOGRAMPLUSC4D.org] [13]. The results of the additive models were used.

1.2.1 Human left ventricle tissue

Samples of cardiac tissue (n=313) were acquired from patients from the Myocardial Applied Genomics Network (MAGNet; www.med.upenn.edu/magnet). Left ventricular free-wall tissue was harvested at the time of cardiac surgery from subjects with heart failure undergoing transplantation and from unused donor hearts. The heart was perfused with cold cardioplegia prior to cardiectomy to arrest contraction and prevent ischemic damage. Tissue specimens were then obtained and frozen in liquid nitrogen. Genomic DNA was extracted using the Gentra Puregene Tissue Kit (Qiagen, CA) according to manufacturer's instructions. Total RNA was extracted using the miRNeasy Kit (Qiagen) including DNAse treatment. RNA concentration and quality was determined using the NanoVue Plus™ spectrophotometer (GE Healthcare) and the Agilent 2100 RNA Nano Chip (Agilent).

DNA samples were genotyped using Affymetrix Genome Wide SNP Array 6.0. We applied quality control (QC) filters to exclude unreliable samples, samples with cryptic relatedness and samples that were not genetically inferred Caucasian. For the analysis reported here, we eliminated SNPs with genotype call rate < 95%, with minor allele frequency (MAF) < 15%, or if there was significant departure from Hardy-Weinberg equilibrium ($p < 10\text{-}6$). A total of 360,046 SNPs passed QC and were available for analysis. To improve cross study comparisons, genotype imputation was performed using the Minimac (v 2012.11.16) program[14]. Imputation results were filtered at an imputation quality threshold of 0.5 and a MAF threshold of 0.15. For imputed genotypes, we used dosage value as genotype. To assess gene expression, RNA was hybridized with Affymetrix Genechip ST1.1 arrays using manufacturer instructions. CEL

files were normalized with robust multiarray analysis (RMA) using Bioconductor[15]. To remove potential batch effects, expression values were further adjusted using ComBat[16].

We tested whether an association existed between the genotype of the 41 echocardiographic trait SNPs and gene expression of proximal (or neighboring) genes. A *cis* eQTL analysis was performed using transcripts +/- 1Mb from each of the 41 SNPs using a linear regression model and adjusted for multiple comparisons using a Bonferroni correction (total of 687 SNP-transcript association tests examined). Our analysis used a joint-effects model that allowed for different strengths of association in comparatively healthy hearts from unused donors versus those with end-stage heart failure. Specifically, we fit linear regression models, Y = age + sex + study site + D + β1(g) + β2(g x D), where Y is the log2 transformed expression level of a given expression trait, g is the dosage value of the test SNP, and D is the patient group (D = 1 for heart failure and D = 0 for unused donors). Association between Y and g was assessed by testing H0: β1 = β2 = 0 using a likelihood ratio test. Significance of the test statistic was evaluated by comparing with a Chi-squared distribution with two degrees of freedom. We considered P < 7.50 x 10-5 (0.05/687 tests) to be statistically significant. To test whether statistically significant associations were likely to be mediated through the strongest eSNPs in the region, we fit analogous models that conditioned on genotypes for the strongest observed cis eSNP for each transcript. Echocardiographic SNPs that showed substantial attenuation of the strength of association with a specific transcript upon adjustment for the best eSNP for that transcript suggest that the

echocardiographic trait association is mediated by influence of the causal variant (not necessarily the SNP identified) on expression of that gene.

1.2.2 Whole blood

In 5,311 human whole blood samples of the results of Westra et al.[17], all transcripts of which the center of the corresponding array probe is located within 250 kb of the SNP position were correlated with each replicated SNP.

1.2.3 Monocytes

In an expression dataset of human monocytes from 1,372 participants of the GHS[18], relation of SNPs to the gene expression was calculated by linear regression assuming an additive model adjusted for sex and age. A *cis* association was defined as an association with expression levels of a gene at 250 kb up- or downstream of the SNP position. A significance threshold of 0.001 (Bonferroni correction of $P = 0.01$ for 10 tests) was used to adjust for multiple testing.

1.3 Pathway Analysis

The collective effects of multiple genetic variants on biological systems were investigated by pathway analysis. For each of the ~2.5 million tested SNPs, we assigned an overall score to indicate its association with echo-related traits, which was equivalent to the most significant p-value among the seven structural and systolic traits. These genetic variants were then mapped back to the human reference genome (NCBI Build 36, 2006) and we examined their locations relative to RefSeq genes (Mar 17, 2013). We took a region of 110kb upstream to 40kb downstream of each gene's transcript boundaries and determined SNP with the lowest score within that region [19]. Of

the 23,696 genes evaluated, 379 reached a score less than 1.0×10^{-5}. These genes were then imported into Ingenuity IPA for pathway analysis (Ingenuity Systems, Redwood, CA). Fisher's exact test was used to justify the enrichment of each of the canonical pathways, and false discovery rate (FDR) was used to adjust for multiple testing [20]. Our analysis reveals that four canonical pathways were significantly enriched (FDR<0.05) with echo related genes, including the protein kinase A signaling pathway, death receptor Signaling, the Wnt/Ca+ pathway and the P2Y purigenic receptor signaling pathway. The results suggest that the disruption of these signaling pathways might be the potential mechanisms affecting echo traits.

We also combined the association with both systolic and diastolic traits, and performed pathway analysis. Protein kinase A signaling remained the most significant pathway in the combined analysis (*P* value: 5.9×10^{-7}). The other three pathways, death receptor signaling pathway (*P* value: 2.2×10^{-3}), Wnt/Ca+ pathway (*P* value: 2.8×10^{-3}), and P2Y purigenic receptor signaling pathway (*P* value: 1.0×10^{-2}), also retained nominal significance although p-values were attenuated. None of the pathways reached the FDR cutoff for the diastolic traits alone.

We then examined the interactions between the top echo-related loci by DAPPLE[21]. Variants with *P* value less than 5×10^{-7} were used as the input of DAPPLE software, which then built both direct and indirect interaction networks from seed genes nearby the top loci. No significant interactions were found between loci (*P* value: 0.68 for direct interactions, and *P* value: 0.51 for indirect interactions). The analysis by SNIPPER (http://csg.sph.umich.edu/boehnke/snipper/) did not find direct interactions between the top echo-related loci.

The potential regulatory effect of the top loci was also investigated using all tissue types represented in the ENCODE data[22]. Seven loci were found be located within enhancer histone marks (rs1454157, rs10774625, rs6702619, rs1532292, rs17608766, rs11207426, and rs9470361). In addition, seven loci were located within DNase hypersensitive sites in multiple cell lines, suggesting that these loci might be involved into important regulatory processes in different developmental stages.

We also used the DEPICT tool to further explore functionality of the identified SNPs[23]. SNPs within the major histocompatibility complex region were excluded (chromosome 6, base pairs 25,000,000 through 35,000,000). LD $r^2 > 0.5$ distance was used to define locus boundaries yielding 54 loci for AoD and 27 loci for LVD comprising 83 and 55 genes, respectively. DEPICT was run using default settings, that is using 500 permutations for bias adjustment, 20 replications for false discovery rate estimation, normalized expression data from 77,840 Affymetrix microarrays for gene set reconstitution (see ref.[24] for details), 14,461 reconstituted gene sets for gene set enrichment analysis, and testing 209 tissue/cell types assembled from 37,427 Affymetrix U133 Plus 2.0 Array samples for enrichment in tissue/cell type expression.

2 SUPPLEMENTAL MATERIAL

2.1 Abbreviations of participating cohorts

AortaGen	AortaGen Consortium
AGES	Age, Gene/Environment Susceptibility
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial
ASPS	Austrian Stroke Prevention Study
CARDIA	Coronary Artery Risk Development in Young Adults
CARLA	Cardiovascular Disease, Living and Ageing in *Halle*
CHARGE-HF	Cohorts for Heart and Aging Research in Genomic Epidemiology – Heart Failure Working Group
CHS	Cardiovascular Health Study
Cilento	Genetic Park of Cilento and Vallo di Diano Project
FHS1, FHS2, FHS3	Framingham Heart Study, original cohort, offspring and third generation cohorts
Generation R	Generation R Study
GHS-I, -II, -III	Gutenberg Health Study, waves 1-3
HyperGEN	Hypertension Genetic Epidemiology Network
JHS	Jackson Heart Study
KNHI	Kompetenznetz Herzinsuffizienz (Competence Network Heart Failure)
KORA-F3, -F4	Cooperative Health Research in the Region of Augsburg, waves 3 and 4
LURIC	Ludwigshafen Risk and Cardiovascular Health Study
MICROS	Microisolates in South Tyrol Study
MPP	Malmö Preventive Project
NOMAS	Northern Manhattan Study
PIVUS	Prospective Investigation of the Vasculature in Uppsala Seniors
RSI, -II, -III	Rotterdam Study, subcohorts 1-3
SHIP	Study of Health in Pomerania
SHIP-Trend	Study of Health in Pomerania, independent baseline cohort
ULSAM	Uppsala Longitudinal Study of Adult Men
YFS	The Cardiovascular Risk in Young Finns Study

2.2 Description of cohorts (Table S1)

Table S 1: General cohort descriptives

Cohort / study	Study Design	Total sample size of cohort	Country	Inclusion / exclusion criteria for this analysis	Reference
AGES	Population-based	5,660	Iceland	Sample exclusion criteria included sample failure, genotype mismatch with reference panel, and sex mismatch, resulting in clean genotype data on 3,219 individuals.	[25]
ASCOT	Substudy of ASCOT clinical trial (ASCOT-HACVD)	885	Ireland, UK	Samples with CNV370 genotype data and part of the ASCOT-HACVD study were included in the study. Samples with genotype call rate <95% were excluded from the genetic association study.	[26]
ASPS	Community-based prospective cohort study	2,007	Austria	Non-European ancestry not included, sample failures, genotyped sex different from recorded sex	[27]
CARDIA	Prospective Cohort Study	5,115	US	Non-caucasian participants excluded	[28]
CARLA	Prospective, population-based	1,779	Germany	Subjects with successful genotyping and available echocardiography measurements, exclusion of subjects of the baseline examination (2002-2006) due to missing echocardiographic variables.	[29]
CHS	Prospective, population-based	5,888	US	Samples in this analysis were limited to those of European ancestry, those with successful genotyping and available echocardiography measurements.	[30]
Cilento	Cross-sectional Isolated Population Study	2,137	Italy	Echocardiography and genotyping data available	[31,32]
FHS1	Prospective family-based	5,209	US	Echo available and person free of MI and CHF at exam cycle 20.	[33]
FHS2	Prospective family-based	5,124	US	Echo available and person free of MI and CHF for at least two exam cycles (2,4,5,6).	[34]
FHS3	Prospective family-based	4,095	US	Free of MI and CHF with echo data available at exam 1.	[35]
Generation R	Population-based cohort	9,901	The Netherlands	Inclusion: Caucasian, live birth, Exclusion: twins	[12]
GHS-I, -II, -III	Population-based	GHS-I 3,192 GHS-II 1,179 GHS-III 9,750	Germany	Missing echocardiographic traits or genetic data	[36]
HyperGEN	Population-based family study	2,407	US	Samples in this analysis were restricted to Caucasian families.	[37]

Table S 1, continued

Cohort / study	Study Design	Total sample size of cohort	Country	Inclusion / exclusion criteria for this analysis	Reference
JHS	Prospective and Community based study	3,029	US	Missing Echocardiographic traits in the first examination visit (2000-2004)	38
KNHI	Prospective population-based cohort at high CV risk	1,732	Germany	Excluded were: 1) atrial fibrillation at investigation 2) Non-Caucasian, sex mismatch, relatedness to other study participant, individual call rate < 90%	39
KORA-F3	Population-based	3006	Germany	participants between 35 and 79 years with echocardiograms, genome-wide association data and free of prevalent MI and CHF (n=589)	40-42
KORA-F4	Population-based	4,261	Germany	Participants between 25 and 74 years with echocardiograms, genome-wide association data and free of prevalent MI and CHF (n=373)	40-42
LURIC	Case-control	3,316	Germany	Availability of genotypes	43
MICROS	Population-based	1,340	Italy	None	44
MPP	Prospective population-based cohort, with oversampling of subjects with impaired glucose tolerance and diabetes	1,791	Sweden	Echocardiography and DNA available.	45
NOMAS	Population-based incidence and case-control study	3,298	US	Samples with call rate ≤95%, mismatch between genotyped gender and self-reported gender, genetic ancestry outliers (samples beyond 6 SD from the mean of PC1-10 in each racial group), and one from each pair of samples with PI_HAT≥0.25 were removed from analysis.	46
PIVUS	Prospective population-based study	1,016	Sweden	Sample call rate <95%, genotype heterozygosity > +-3 standard deviations, gender discordance, and duplicates.	47
RS-I	Prospective population-based cohort study	7,983	the Netherlands	Inclusion: Availability of GWAs data and phenotype data. Exclusion: Sample call rate < 97.5%, excess autosomal heterozygosity, mismatch between called and phenotypic gender, ethnic outliers identified by the IBS clustering analysis with >4 standard deviations from population mean or IBS probabilities >97%, familiar relationships	48
RS-II	Prospective population-based cohort study	3,011	the Netherlands	Inclusion: Availability of GWAs data and phenotype data. Exclusion: Sample call rate < 97.5%, excess autosomal heterozygosity, mismatch between called and phenotypic gender, ethnic outliers identified by the IBS clustering analysis with >4 standard deviations from population mean or IBS probabilities >97%, familiar relationships	48

Table S 1, continued

Cohort / study	Study Design	Total sample size of cohort	Country	Inclusion / exclusion criteria for this analysis	Reference
RS-III	Prospective population-based cohort study	3,932	the Netherlands	Inclusion: Availability of GWAs data and phenotype data. Exclusion: Sample call rate < 97.5%, excess autosomal heterozygosity, mismatch between called and phenotypic gender, ethnic outliers identified by the IBS clustering analysis with >4 standard deviations from population mean or IBS probabilities >97%, familiar relationships	[48]
SHIP	Prospective population-based study	4308 (SHIP-0) 3300 (SHIP-1)	Germany	Excluded arrays with CallRate < 92%, duplicate samples (by estimated IBD) and individuals with reported/genotyped gender mismatch. For diastolic analyses data from the first 5-year follow-up were used (3300 total sample / 2400 with echo and genotyping data).	[49]
SHIP-Trend	Prospective population-based study	4,420	Germany	Excluded arrays with CallRate < 94%, duplicate samples (by estimated IBD) and individuals with reported/genotyped gender mismatch	[49]
ULSAM	Prospective population-based study	1,221	Sweden	Sample call rate <95%, genotype heterozygosity > +-3 standard deviations, gender discordance, and duplicates.	[50]
YFS	Prospective population-based study	2,063	Finland	Genotyping sample call rate < 95 %, excess heterozygosity, duplicates, cryptic relatedness, MDS outliers , gender mismatch	[51]

2.3 Baseline characteristics of cohorts (Table S2)

Table S 2: Selected characteristics of participants

Cohort / study	AGES	ASCOT	ASPS	CARDIA	CHS	FHS		FHS-3	GHS-I	GHS-II	GHS-III	HyperGEN
Age, y mean (SD)	76 (6)	64 (8)	66 (8)	31 (3)	75 (5)	74.9 (4.9)	51.7 (9.7)	40.16 (8.86)	56 (11)	55 (11)	55 (11)	50 (14)
Age range, y	67-95	40-80	49-90	22-37	65-96	68-93	26-79	19-72	35-74	36-74	35-74	18 - 87
Female sex, No. (%)	315 (57)	336 (22)	462 (57)	849 (53)	1981 (60)	430 (60)	1746 (54)	2050 (53.1)	1558 (49)	590 (50)	4797 (49)	639 (50.4)
Height, cm mean (SD)	167 (10)	170 (9)	166 (9)	171 (9)	164 (9)	162 (10)	168 (9)	171 (9)	171 (9)	169 (10)	170 (10)	170 (9)
Weight, kg mean (SD)	75 (14)	85 (15)	73 (13)	73 (16)	72 (14)	70 (14)	76 (16)	79 (19)	79 (16)	79 (17)	80 (17)	85 (19)
BMI, kg/m^2 mean (SD)	26.9 (4.2)	29.4 (4.7)	26.8 (4.1)	24.9 (4.6)	26.4 (4.4)	26.7 (4.4)	26.9 (4.7)	26.9 (5.5)	27.2 (4.8)	27.3 (5.0)	27.5 (5.1)	29.4 (6.1)
Obesity, No (%)	110 (20)	336 (38)	154 (19)	189 (12)	568 (17)	138 (19)	593 (18)	877 (23)	761 (24)	298 (25)	2516 (26)	513 (40.4)
Systolic BP, mmHg mean (SD)	143 (21)	135 (11)	143 (22)	106 (11)	133 (20)	147 (23)	125 (15)	117 (14)	134 (18)	131 (17)	131 (17)	123.5 (19)
Hypertension, No. (%)	430 (78)	885 (100)	281 (34)	63 (4)	1512 (47)	524 (74)	870 (27)	718 (19)	1692 (53)	570 (48)	4786 (49)	659 (52)
Smoking, No. (%)	59 (11)	207 (23)	95 (11)	350 (22)	221 (7)	74 (10)	619 (20)	671 (17)	585 (18)	249 (21)	1910 (20)	116 (9)
Diabetes, No. (%)	72 (13)	165 (19)	74 (9)	30 (2)	272 (8)	42 (6)	130 (4)	116 (3)	237 (7)	90 (8)	735 (8)	165 (13)

Table S 2, continued

Cohort / study	KNHI	KORA-F3	KORA-F4	MICROS	PIVUS	RS-I	RS-II	RS-III	SHIP	SHIP-Trend	ULSAM
Age, y mean (SD)	64 (9)	62 (10)	58 (8)	46 (17)	75 (0)	75 (6)	68 (7)	56 (6)	54 (6)	50 (14)	71 (1)
Age range, y	50-85	35-79	25-74	19-83	75-76	65-99	58-98	46-97	25-86	20-81	69.7-73.3
Female sex, No. (%)	315 (56)	290 (56)	201 (54)	110 (64)	282 (55)	1465 (59)	955 (56)	988 (56)	1825 (52)	554 (56)	0 (0)
Height, cm mean (SD)	167 (10)	167 (9)	167 (9)	170 (8)	168 (9)	166 (9)	168.0 (9)	171 (9)	169 (4)	170 (9)	175 (6)
Weight, kg mean (SD)	79 (15)	77 (13)	77 (13)	70 (13)	75 (14)	76 (13)	78.5 (14)	81 (16)	79 (17)	79 (15)	80 (12)
BMI, kg/m^2 mean (SD)	28.5 (7.7)	27.0 (4.0)	26.9 (4)	24.2 (3.7)	26.9 (4.4)	27.4 (4.1)	27.8 (4.0)	27.7 (4.7)	27.8 (4.8)	27.3 (4.6)	26.3 (3.4)
Obesity, No (%)	162 (29)	114 (22)	82 (22)	10 (5)	177 (21)	537 (23)	404 (25)	419 (24)	895 (26)	255 (26)	155 (13)
Systolic BP, mmHg mean (SD)	145 (24)	133 (19)	135 (20)	N/A	149 (19)	153 (21)	145 (20)	133 (19)	137 (21)	124 (17)	147 (19)
Hypertension, No. (%)	422 (79)	106 (18)	75 (20)	N/A	746 (83)	2133 (87)	1208 (74)	824 (47)	901 (26)	391 (40)	909 (75)
Smoking, No. (%)	251 (45)	112 (19)	67 (18)	N/A	51 (6)	298 (12)	275 (16)	467 (27)	955 (27)	216 (22)	245 (21)
Diabetes, No. (%)	108 (19)	N/A	N/A	N/A	126 (15)	329 (14)	180 (11)	119 (7)	278 (8)	31 (3)	131 (11)

Table S 2, continued

Cohort / study	CARLA	Cilento	MPP	YFS	Generation R	JHS	NOMAS
Age, y mean (SD)	67 (10)	53 (19)	68 (6)	42 (5)	6 (0)	55 (13)	70 (9)
Age range, y	50 - 87	12-98	56-79	34-49	5-9	21-93	41-97
Female sex, No. (%)	636 (45)	745 (56)	525 (29)	937 (55)	1025 (49)	1109 (62)	653 (59)
Height, cm mean (SD)	167 (9)	162.0 (10)	171.6 (9)	172 (9)	120 (6)	169 (9)	162 (10)
Weight, kg mean (SD)	79 (15)	70 (14)	83.5 (15)	79 (17)	23 (3)	92 (22)	75 (14)
BMI, kg/m^2 mean (SD)	28.3 (4.5)	26.5 (4.8)	28.3 (4.3)	26.5 (5.0)	15.9 (1.4)	32.0 (7.5)	28.7 (5.1)
Obesity, No (%)	998 (71)	271 (20)	172 (10)	347 (20)	32 (1)	931 (52)	383 (35)
Systolic BP, mmHg mean (SD)	138 (20)	124.2 (14)	148 (20)	119 (14)	102.1 (7.9)	127 (18)	138 (19)
Hypertension, No. (%)	1140 (81)	569 (42)	1419 (80)	141 (8)	3 (0)	56 (1003)	726 (66)
Smoking, No. (%)	197 (14)	281 (21)	325 (18.1)	347 (20)	N/A	235 (13)	174 (16)
Diabetes, No. (%)	275 (20)	124 (9)	633 (35.3)	40 (2)	0 (0)	286 (17)	219 (19.9)

2.4 Echo methods (Table S3)

Table S 3: Echo methods used by cohorts

Cohort / study	Echo device	LVEF method (as exclusion criteria for diastolic traits) 1= LVEF (Simpson) 2= LVEF (Teichholz) 3=Fractional shortening 4= visual estimation	Definition of binary diastolic traits used 1= tissue imaging 2= pulmonary venous inflow and mitral inflow at peak Valsalva maneuver	Reference
AGES	Siemens Medical Systems, Sequoia C256, Acuson	4	1	[52]
ASCOT	ATL, HDI 5000	1 or 2	1	[53]
ASPS	GE Medical, Vingmed CFM 750 and CFM 800	2 or 4	N/A	1
CARDIA	ACUSON 128	N/A	N/A	[54,55]
CARLA	GE Medical, Vivid 5	1, 2 or 3	1	[56,57]
CHS	Toshiba, SSH-160A	4	N/A	[55,58]
Cilento	GE HealthCare, Vivid 3	1	N/A	N/A
FHS1, FHS2, FHS3	Hewlett Packard, 77020AC / Sonos 1000	3 or 4	1	[59]
GenerationR	ATL-Philips, Model HDI 5000 or GE Medical Systems, Logiq E9	N/A	N/A	[60]
GHS-I, -II, -III	Philips, IE33	1	1	[61]
HyperGEN	Acuson 128	2	N/A	[62-64]
JHS	Hewlett Packard 4500	4	2	[65]
KNHI	Hewlett-Packard Sonos 5500	1	2	[66]
KORA-F3, -F4	Hewlett Packard, Sonos 1500	4	1	[1,67]
MICROS	Toshiba, Aplio XG	1	2	N/A
MPP	Acuson, Sequoia or Philips, Sonos 5500	4	1	[45]
NOMAS	Philips, IE33	1 or 4	1	[68]
PIVUS	Accuso, XP128	2	N/A	[69]
RS-I	Esaote Biomedica AU3, Acuson, Cypress; GE, Vivid I (for TDI)	3 or 4	N/A	[70]
RS-II, -III	Acuson, Cypress; GE, Vivid I (for TDI)	3 or 4	N/A	[70]
SHIP	GE Medical, Vingmed CFM 800A	2	2	[49,71]
SHIP-Trend	GE Medical, Vivid i	2	1	[49]
ULSAM	Hewlett Packard, Sonos 1500	2	N/A	[72]
YFS	ACUSON, Sequoia 512	1 or 2	1	N/A

2.5 Echo values by cohorts (Table S4)

Table S 4: Echo values by cohorts

Cohort / study	AoD [73]	LA [73]	LVDD [73]	LVWT [73]	LVM [g]	FS [%]	LVSD [n (%)]
AGES	3.2 (0.5)	3.9 (0.6)	4.4 (0.7)	2.2 (0.5)	168 (54)	32.9 (10.5)	108 (30)
ASCOT	N/A	4.1 (0.6)	4.9 (0.5)	2.5 (0.4)	238 (67)	N/A	N/A
ASPS	3.0 (0.5)	3.8 (0.6)	4.7 (0.6)	2.2 (0.4)	195 (63)	N/A	104 (13)
CARDIA	2.8 (0.4)	3.5 (0.5)	5.0 (0.5)	1.7 (0.3)	146 (43)	35.8 (5.7)	173 (12)
CARLA	3.1 (0.4)	4.0 (0.6)	4.9 (0.7)	2.2 (0.4)	208 (68)	37.6 (7.7)	82 (7)
CHS	3.2 (0.4)	3.9 (0.7)	4.9 (0.6)	1.8 (0.3)	147 (44)	41.8 (7.3)	234 (7)
Cilento	3.4 (0.4)	3.7 (0.4)	4.9 (0.4)	2.0 (0.2)	176 (38)	35.0 (2.7)	N/A
FHS1	N/A	N/A	N/A	N/A	N/A	N/A	N/A
FHS2	3.1 (0.3)	3.8 (0.4)	4.8 (0.4)	1.9 (0.2)	159 (37)	36.5 (4.0)	126 (5)
FHS3	3.1 (0.4)	2.7 (0.5)	4.9 (0.4)	1.8 (0.2)	158 (42)	35.63 (3.3)	60 (2)
Generation R	1.9 (0.2)	N/A	3.8 (0.3)	N/A	N/A	N/A	N/A
GHS-I	N/A	N/A	4.5 (0.5)	2.0 (0.3)	159 (47)	37.5 (6.3)	71 (2)
GHS-II	N/A	N/A	4.6 (0.5)	2.0 (0.3)	157 (49)	36.4 (5.4)	17 (1)
GHS-III	N/A	N/A	4.9 (0.6)	1.9 (0.3)	163 (51)	34.9 (4.2)	116 (1)
HyperGEN	3.4 (0.4)	3.5 (0.6)	5.15 (0.5)	0.8 (0.2)	157 (47)	33.7 (5.3)	151 (12.3)
JHS	3.1 (0.3)	3.6 (0.4)	4.9 (0.4)	1.7 (0.3)	146 (37)	38.8 (6.2)	193 (7)
KNHI	3.2 (0.5)	4.0 (0.6)	4.9 (0.5)	2.2 (0.6)	219 (61)	N/A	N/A
KORA-F3	2.9 (0.4)	3.8 (0.5)	4.8 (0.4)	1.9 (0.3)	163 (38)	N/A	48 (8)
KORA-F4	3.1 (0.4)	3.7 (0.5)	4.7 (0.6)	1.9 (0.5)	158 (63)	38.0 (8.0)	44 (13)
MICROS	3.2 (0.5)	3.7 (0.6)	4.9 (0.6)	N/A	N/A	43.9 (8.8)	N/A
MPP	N/A	4.1 (0.6)	4.8 (0.6)	2.1 (0.3)	179 (54)	N/A	41 (2)
NOMAS	3.1 (0.4)	3.8 (0.5)	4.4 (0.5)	2.3 (0.3)	183 (52)	36.8 (6.9)	N/A
PIVUS	N/A	3.9 (0.7)	N/A	2.7 (0.4)	178 (59)	45.9 (7.9)	30 (4)
RS-I	3.3 (0.4)	4.0 (0.6)	5.0 (0.6)	1.6 (0.3)	144 (43)	37.4 (7.3)	266 (12)
RS-II	3.4 (0.4)	4.0 (0.6)	5.2 (0.5)	1.6 (0.2)	142 (40)	40.8 (5.7)	65 (4)
RS-III	3.3 (0.4)	4.0 (0.5)	5.2 (0.4)	1.5 (0.2)	132 (37)	42.8 (3.9)	5 (0)
SHIP	3.0 (0.4)	3.6 (0.6)	5.0 (0.5)	2.0 (0.4)	188 (15)	37.0 (7.3)	402 (13)
SHIP-Trend	2.8 (0.4)	3.9 (0.6)	4.9 (0.6)	2.0 (0.3)	169 (14)	42.3 (8.4)	47 (5)
ULSAM	N/A	4.3 (0.6)	N/A	N/A	240 (64)	35.9 (7.1)	53 (14)
YFS	3.2 (0.3)	3.5 (0.4)	5.2 (0.5)	1.4 (0.2)	129 (32)	32.1 (2.9)	N/A

Table S 4, continued

Cohort / study	Mv-E [cm/s]	Mv-A [cm/s]	E/A	DecTime [s]	IVRT [s]	E´ [cm/s]	E/E´	DDpEF [n (%)]	HFpEF [n (%)]
AGES	70.9 (17.2)	80.6 (19.6)	0.9 (0.3)	0.27 (0.06)	N/A	9.9 (2.2)	7.5 (2.3)	101 (35)	77 (21)
ASCOT	60.1 (12.7)	70.7 (13.9)	0.9 (0.2)	0.19 (0.04)	N/A	8.0 (1.8)	7.8 (1.9)	N/A	N/A
ASPS	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
CARDIA	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
CARLA	67.2 (17.6)	70.4 (20.5)	1.0 (0.4)	0.30 (0.11)	0.1 (0)	6.2 (1.8)	11.6 (4.4)	411 (29)	26 (2)
CHS	72.0 (15.9)	83.3 (21.4)	0.9 (0.3)	0.25 (0.06)	0.73 (0.29)	N/A	N/A	N/A	N/A
Cilento	70.2 (16.8)	71.2 (18.4)	1.1 (0.4)	0.18 (0.04)	0.10 (0.01)	N/A	N/A	N/A	N/A
FHS1	42.0 (15.8)	60.6 (15.4)	0.7 (0.2)	0.15 (0.05)	N/A	N/A	N/A	N/A	N/A
FHS2	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
FHS3	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Generation R	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
GHS-I	78.4 (18.0)	75.5 (19.0)	1.1 (0.4)	0.23 (0.05)	0.08 (0.03)	11.2 (3.5)	7.6 (2.7)	519 (20)	150 (7)
GHS-II	76.7 (16.8)	74.2 (17.7)	1.1 (0.4)	0.22 (0.04)	0.09 (0.02)	11.2 (3.3)	7.3 (2.4)	180 (19)	44 (5)
GHS-III	78.6 (16.6)	72.7 (19.2)	1.1 (0.4)	0.21 (0.04)	0.45 (0.05)	10.8 (3.1)	8.4 (23.3)	1548 (19)	406 (6)
HyperGEN	62 (16.6)	58.5 (18.0)	1.3 (0.4)	0.186 (0.06)	0.80 (0.02)	N/A	N/A	N/A	N/A
JHS	81.0 (20.0)	84.0 (19.0)	1.2 (0.3)	N/A	0.87 (0.14)	N/A	N/A	N/A	N/A
KNHI	76.5 (20.1)	76.4 (21.2)	1.1 (0.4)	0.24 (0.06)	0.10 (0.02)	8.8 (3.2)	10.0 (5.1)	162 (41)	66 (14)
KORA-F3	72.8 (17.4)	74.1 (15.4)	1.0 (0.3)	0.23 (0.06)	0.11 (0.02)	7.2 (2.0)	10.6 (3.3)	N/A	N/A
KORA-F4	62 .0 (14.9)	66.0 (16.4)	1.0 (0.5)	0.23 (0.07)	0.08 (0.03)	N/A	N/A	N/A	N/A
MICROS	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
MPP	72.2 (17.5)	79.8 (18.2)	0.9 (0.3)	0.22 (0.05)	N/A	7.8 (2.7)	10.3 (4.3)	602 (46)	62 (5)
NOMAS	71.3 (17.7)	89.3 (20.8)	0.8 (0.3)	0.22 (0.05)	N/A	7.3 (1.7)	10.1 (3.4)	367 (62)	36 (14)
PIVUS	60.0 (14.0)	67.6 (17.0)	0.9 (0.3)	N/A	1.11 (0.19)	6.1 (1.3)	10.0 (2.7)	N/A	N/A
RS-I	64.6 (17.3)	78.1 (18.4)	0.8 (0.3)	0.22 (0.05)	N/A	7.1 (8.9)	12.2 (5.0)	N/A	N/A
RS-II	66.5 (14.9)	75.3 (15.9)	0.9 (0.2)	0.21 (0.04)	N/A	7.1 (1.8)	10.4 (3.5)	N/A	N/A
RS-III	70.3 (15.2)	66.0 (13.9)	1.1 (0.3)	0.19 (0.03)	N/A	N/A	N/A	N/A	N/A
SHIP	68.8 (15.7)	62.2 (15.7)	1.2 (0.4)	0.17 (0.42)	0.09 (0.02)	N/A	N/A	334 (16)	37 (2)
SHIP-Trend	61.0 (15.0)	63.0 (14.4)	1.2 (0.4)	0.17 (0.03)	0.88 (0.02)	13.3 (3.9)	5.7 (1.7)	63 (9)	5 (0)
ULSAM	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
YFS	76.9 (13.0)	51.4 (11.3)	1.5 (0.4)	0.22 (0.04)	0.11 (0.02)	16.2 (2.7)	4.8 (1.0)	N/A	N/A

Echo values for subjects with echo and genotyping data. Numbers are mean (SD) or numbers (percentage). LV= left ventricular; LVDD= LV diastolic dimensions; LVWT= LV wall thickness; LA= left atrial; FS= fractional shortening; LVSD= LV systolic dysfunction; E= Peak velocity of the mitral E-wave; A= Peak velocity of the mitral A-wave; E/A= Ratio of the mitral E- and A-wave; E/A_val= Ratio of the mitral E- and A-wave during Valsalva maneuver; Dec time= Deceleration time of the mitral E-wave; IVRT= Isovolumetric relaxation time; E´= Peak velocity of the excursion of the lateral mitral annulus in the early diastolic phase; E/E´= Ration of E and ´E; S= systolic pulmonary venous forward flow; D= diastolic pulmonary venous forward flow; S/D= ratio of systolic and diastolic pulmonary venous flow (S/D); DDpEF= Diastolic Dysfunction with preserved ejection fraction; HFpEF= Heart failure with preserved ejection fraction.

2.6 Genotyping Methods and Imputation (Table S5)

Table S 5: Genotyping information by cohorts

Cohort / study	Array type	Genotype calling	QC filters for genotyped SNPs used for imputation	No of SNPs used for imputation	Imputation software	Imputation Backbone for phased CEU haplotypes (NCBI build)	Filtering of imputed genotypes	Data management and statistical analysis	Population stratification or Principal Components
AGES	Illumina 370CNV	Illumina BeadStudio	call rate < 97% pHWE< 1 x 10-6, mishap (PLINK haplotype-based test for non-random missing genotype data[2]) p < 1 x 10-9, and mismatched positions between Illumina, dbSNP and/or HapMap	325,094	MACH version 1.0.16	HapMap, release 22 (build 36)	None	ProABEL	None
ASCOT	Illumina HumanCNV370-Duo	Illumina BeadStudio	CR<0.97, MAF<0.05, HWE_pvalue<1e-07	283,291	BEAGLE	HapMap II release 24 CEU reference panel	Information score<0.6, MAF<5%	PLINK, R	Adjusted for first 10PCs
ASPS	Illumina Human 610-Quad BeadChip	Illuminus	call rate <97.5%, MAF <1%, , pHWE <1E-6	550,635	MACH v1.0.15	HapMap, release 22 (build 36)	None	SPSS, ProbABEL, R	None
CARDIA	Affymetrix 6.0	BEAGLE, Birdseed	call rate <95%, MAF<3%, pHWE <10E-4	579,630	BEAGLE	HapMap, release 22 (build 36)	Rsq<0.3, MAF<1%	ProbABEL, PLINK, R	None
CARLA	ABI	N/A	N/A	N/A	N/A	NCBI built 37	N/A	R version 2.14.1	None
CHS	Illumina 370CNV BeadChip system	Illumina BeadStudio	call rate < 97%, HWE P < 10-5, > 2 duplicate errors or Mendelian inconsistencies (for reference CEPH trios), heterozygote frequency = 0, SNP not found in HapMap.	306,655	BIMBAM v0.99	HapMap, release 22 (build 36)	SNPs were excluded for variance on the allele dosage ≤0.01	R, robust SE estimates	None

Table S 5, continued

Cohort / study	Array type	Genotype calling	QC filters for genotyped SNPs used for imputation	No of SNPs used for imputation	Imputation software	Imputation Backbone for phased CEU haplotypes (NCBI build)	Filtering of imputed genotypes	Data management and statistical analysis	Population stratification or Principal Components
Cilento	Illumina 370K (n=859) Illumina OmniExpress(n=758)	Illumina BeadStudio	Imputation was performed using the following filters: SNPs in common between the two arrays, call rate<95%, MAF<1%. For the directly typed SNPs in common between the two groups, the real genotype was used in the association analysis, while the imputation dosage was considered for the other SNPs.	190862	MACH, minimac	1000G Phase I integrated Release Version 3 (build 37)	None	R, linear model, GenABEL and ProbABEL (mmscore function was used to account for relatedness)	none
FHS1, FHS2, FHS3	Affymetrix 500K; Affymetrix 50K supplemental	BRLMM	pHWE<1e-6, call rate<97%, mishap p<1e-9, MAF<0.01, Mendelian errors>100, SNPs not in Hapmap or strandedness issues merging with Hapmap	378,163	MACH version 1.0.15	HapMap, release 22 (build 36)	None	R, linear mixed effect models and GEE models, robust variance option to account for relatedness	Adjused for first PC estimated from Eigenstrat associated with calcium levels (*P* <0.05).(35)
Generation R	Ilumina 610 Quad and 660W	Genomestudio 2009 V.1.1.9	call rate <98%, MAF <1%, pHWE <10E-6	492.871	MACH and mini-mac	HapMap release 22	None	MACH2QTL	Adjusted for the first 4 PC's
GHS-I, -II, -III	Affymetrix SNP 6.0	Birdseed2	call rate ≤98%, MAF ≤0.01 and pHWE≤0.0001	662,405 (GHS-I) 673,914 (GHS-II)	IMPUTE v2.1.0	HapMap, release 24 (build 36)	None	MetABEL, R	None
HyperGEN	Affymetrix 5.0	Birdsuite	monomorphic SNPs, X-chromosomem SNPs, non-Mendelian inheritance errors, missing rate >5%, MAF<1%,Hardy-Weinberg p-value <10-6	358327	MACH	HapMap, release 22 (build 36)	Rsq<0.3, MAF<1%, MAF<1%, HWP <10-6	R, LMEKIN package	Adjusted for 10 PCs
JHS	Affymetrix SNP 6.0	Birdseed2	pHWE<1e-6, call rate<95%, MAF<0.01, Imputation quality >0.30	868,969 (JHS) 796,384 (ARIC-JHS)	MACH version 1.0.16	HapMap, release 22 (build 36)	None	ProbABEL	Adjusted for the first 10 PCs

Table S 5, continued

Cohort / study	Array type	Genotype calling	QC filters for genotyped SNPs used for imputation	No of SNPs used for imputation	Imputation software	Imputation Backbone for phased CEU haplotypes (NCBI build)	Filtering of imputed genotypes	Data management and statistical analysis	Population stratification or Principal Components
KNHI	Affymetrix 500K (n= 127), Affymetrix 5.0 (n= 17) Affymetrix 6.0 (n = 417)	Affy 500K: BRLMM Affy 5.0: BRLMM-P Affy 6.0: Birdseed2	per chip type: SNP call rate <95%, MAF <0.01, pHWE <10-5; in sample: SNP call rate <90%; exclusion of SNPs with discordance rates >5% between chip types, exclusion of discordant genotypes for subjects typed on >1chip	SNPs with call rate >90% in sample: 384,234 (out of 736,307)	MACH	"HapMap, release 22 (build 36) dbSNP 126	None (QC filters on meta-level: RSQ < 0.6)	PLINK, R, linear models with ProbABEL, GenABEL	None (subjects excluded if related, wrong ethnicity, sex-mismatch, or individual call rate <90%)
KORA-F3	Affymetrix 500K	BRLMM	pHWE<1e-6, individual call rate<93%, snp call rate<95%, MAF<0.01	379,392	Impute v1.0.0	HapMap, release 22 (build 36)	None	R, linear models	None
KORA-F4	Affymetrix 6.0	Birdseed2	On chip level only subjects with overall genotyping efficiencies of at least 93% were included resulting in an average genotyping efficiency of 93% per chip. In addition the called sex had to agree with the sex in the KORA study database.	630,550	MACH v1.0.16	HapMap, release 22 (build 36)	None	R, MACH2QTL, ProbABEL	None
LURIC	Affymetrix 6.0	Birdseed2	pHWE<1e-4, individual call rate<95%, snp call rate<98%, MAF<0.01	686,195	MACH v1	HapMap, release 22 (build 36)	None	PLINK, R, SPSS	None
MAGNet	Affymetrix 6.0	Birdseed2	genotype call rate > 95% minor allele frequency (MAF) > 15% Hardy-Weinberg equilibrium (p > 10-6)	360,046	Minimac (v2012.11.16) program	N/A	imputation quality threshold of 0.5 and a MAF threshold of 0.15	PLINK,R	None
MICROS	HumanHap 300v2	Illumina BeadStudio	call rate <98%, MAF <1%, pHWE <10E-6	290,356	MACH v1	HapMap, release 22 (build 36)	None	ProbABEL,mmscore argument	None
MPP	Sequenom MassArray iPlex	MassArray Typer 4.0	N/A	N/A	N/A	N/A	N/A	SAS 9.2	None

Table S 5, continued

Cohort / study	Array type	Genotype calling	QC filters for genotyped SNPs used for imputation	No of SNPs used for imputation	Imputation software	Imputation Backbone for phased CEU haplotypes (NCBI build)	Filtering of imputed genotypes	Data management and statistical analysis	Population stratification or Principal Components
NOMAS	Affymetrix SNP 6.0	Affymetric Power Tools	call rate<95%, pHWE<1e-6	804,944 (Black) 815,972 (Hispanic) 795,588 (White)	IMPUTE 2	1000 Genomes phase 1, version 3 reference panel	None	SAS, PLINK	Adjusted for PCs estimated using Eigenstrat (first 2 PCs for Hispanics, first PC for Blacks and Whites)
PIVUS	Human Omni Express and Metabochip	Illumina BeadStudio	For SNPs with MAF >=0.05: pHWE<1e-6, call rate<95%; For SNPs with MAF <0.05: pHWE<1e-6, call rate<99%; MAF<0.01	738,879	IMPUTE version 2.1.2	HapMap, release 22 (build 36)	None	SNPTEST	Adjusted for the first 2 PCs estimated from MDS using PLINK
RS-I,-II, -III	550K (RS-I and RS-II) and 610K (RS-III) Illumina arrays	Illumina BeadStudio Genecall	pHWE<1e-6, SNP call rate<97.5%, MAF<0.01	RS-I: 512,349; RS-II: 466,389; RS-III: 514,073	MACH	HapMap, release 22 (build 36)	None	R, ProbABEL	None
SHIP	Affymetrix SNP 6.0	Birdseed2	None	869,224	IMPUTE v0.5.0	HapMap, release 22 (build 36)	duplicate RSID but different positions	QUICKTEST version 0.95 (Params: --method-score), InforSense, InterSystems Caché	We observed no population stratification using principle components estimated using Eigenstrat. [Rice et al. PMID: 16862161]
SHIP-Trend	Illumina Human Omni 2.5	GenomeStudio Genotyping Module v1.0	excluded: pHWE <= 0.0001 or CallRate <= 0.9 or monomorphic SNPs	1,782,967	IMPUTE v2.1.2.3	HapMap, release 22 (build 36)	duplicate RSID but different positions	QUICKTEST version 0.95 (Params: --method-score), InforSense, InterSystems Caché	We observed no population stratification using principle components estimated using Eigenstrat. [Rice et al. PMID: 16862161]
ULSAM	Human Omni Express and Metabochip	Illumina BeadStudio	For SNPs with MAF >=0.05: pHWE<1e-6, call rate<95%; For SNPs with MAF <0.05: pHWE<1e-6, call rate<99%; MAF<0.01	738,879	IMPUTE	HapMap, release 22 (build 36)	None	SNPTEST	Adjusted for the first 2 PCs estimated from MDS using PLINK
YFS	Illumina 670k	Illuminus	call rate <95%, MAF<1%, pHWE <10E-6	546,677	SHAPEIT v1, IMPUTE v2.2.2	1000 Genomes Phase I (build 37)	None	R, SNPTEST	None

3 Additional tables and figures (Table S6-S19, Figures S1-S20)

Table S 6: Individual study lambdas for left ventricular structure and systolic function echocardiographic traits

Study	AoD	LA	LVDD	LVWT	LVM	FS	LVSD
AGES	1.01	1.03	0.99	0.98	1.00	1.02	1.00
ASCOT	NA	1.01	1.01	0.99	0.94	NA	NA
ASPS	1.01	1.02	0.99	1.01	0.99	NA	1.01
CARDIA	1.02	0.99	0.99	1.00	1.01	1.00	1.02
CHS	1.03	1.09	1.02	1.00	1.02	1.01	1.01
FHS-2	1.03	1.04	1.01	1.03	1.04	1.01	0.99
FHS-3	1.03	1.02	1.02	1.03	1.03	1.03	1.03
GHS-I	NA	NA	1.01	1.02	1.01	1.01	1.01
GHS-II	NA	NA	1.00	1.01	1.01	1.00	0.99
HyperGen	1.10	1.08	1.12	1.16	1.10	1.10	1.10
KNHI	1.00	1.02	1.01	1.01	0.99	NA	NA
KORA-F3	1.00	1.01	1.00	1.00	0.99	0.99	1.01
KORA-F4	1.01	1.01	1.02	1.00	1.00	1.01	0.99
MICROS	1.01	1.02	1.03	1.02	NA	1.01	NA
PIVUS	1.01	1.00	1.02	1.01	1.02	0.98	0.97
RS-I	1.02	1.02	1.00	1.01	1.01	1.01	1.01
RS-II	0.98	1.01	1.00	0.98	1.00	1.00	0.99
RS-III	1.03	1.03	1.03	1.02	1.04	1.01	NA
SHIP	1.02	1.02	1.01	1.02	0.99	1.02	1.01
SHIP-Trend	1.01	1.01	1.02	1.00	1.01	1.00	0.99
ULSAM	NA	1.02	NA	NA	1.00	1.00	1.03

Table S 6, continued: Individual study lambdas for left ventricular structure and systolic function echocardiographic traits

Study	Mv-E	Mv-A	E/A	DecTime	IVRT	E´	E/E´	DDpEF	HFpEF
AGES	0.99	0.99	1.00	1.02	NA	0.99	0.97	1.01	1.00
ASCOT	1.01	0.99	1.01	1.01	NA	1.01	1.00	NA	NA
CARDIA	1.00	1.00	1.01	NA	1.01	NA	NA	NA	NA
CHS	1.02	1.01	1.01	1.03	1.02	NA	NA	NA	NA
FHS-1	1.02	1.03	1.01	1.03	NA	NA	NA	NA	NA
GHS-I	1.01	1.01	1.00	1.01	1.00	1.02	1.02	1.02	1.00
GHS-II	1.01	1.003	1.01	1.01	0.99	1.01	1.01	1.00	0.99
HyperGen	1.16	1.11	1.01	1.09	1.07	NA	NA	NA	NA
KNHI	1.00	0.99	0.99	1.02	0.99	0.99	1.00	1.03	0.94
KORA-F3	1.01	1.01	1.01	1.01	1.04	1.00	1.00	1.02	1.05
KORA-F4	1.00	0.99	1.01	NA	0.99	NA	NA	NA	NA
PIVUS	1.00	1.01	1.01	NA	1.02	1.01	1.02	NA	NA
RS-I	1.01	1.02	1.02	1.01	NA	1.01	1.01	NA	NA
RS-II	1.01	1.01	0.98	0.98	NA	NA	NA	NA	NA
RS-III	1.02	1.02	1.03	1.00	NA	NA	NA	NA	NA
SHIP	1.00	1.01	1.01	1.01	1.02	NA	NA	0.99	1.02
SHIP-Trend	1.00	1.00	1.01	1.01	1.00	1.00	NA	1.03	NA

Table S 7: Meta-analysis results of SNPs per phenotype with a *P* value < 10^{-4} and MAF < 0.01 (LVSD: MAF < 0.03)

See Supplemental Excel file “Supplemental Table 7.xls”

Table S 8: Lookup of novel findings for left ventricular structure and systolic function echocardiographic traits in Caucasian children and generalizability to different ethnicities

	Subpopulation			Caucasian Children*			Hispanics				African Americans Northern Manhattan Study & Jackson Heart Study				
	Cohort			Generation R			Northern Manhattan Study								
Trait	**SNP**	**Chr**	**Effect/ non-effect allele**	**EAF**	**Effect (SE)**	***P* value**	**N**	**EAF**	**Effect (SE)**	***P* value**	**N**	**EAF[1]**	**Effect (SE)**	***P* value**	**N**
AoD, cm	rs806322	13	A/G	0.61	***-0.017* (0.005)**	**6.65×10^{-4}***	2070	0.49	0.009 (0.020)	0.638	515	0.48	*-0.01* (0.01)	0.54	1300
	rs6702619	1	G/T	0.48	*0.011* (0.005)	**0.024**	2070	0.28	*0.017* (0.020)	0.408	515	0.14	*0.03* (0.02)	0.19	1300
	rs17696696	16	G/T	0.60	*-0.002* (0.005)	0.676	2070	0.49	*-0.008* (0.019)	0.682	515	0.34	*-0.02* (0.01)	0.07	1300
	rs7127129	11	G/A	0.42	*-0.006* (0.005)	0.260	2070	0.29	*-0.031* (0.021)	0.130	515	0.18	*-0.01* (0.02)	0.62	1300
	rs17608766	17	C/T	0.15	*0.019* (0.007)	**5.92×10^{-3}**	2070	0.09	*0.003* (0.039)	0.934	515	0.03	*0.07* (0.04)	0.05	1300
	rs4765663	12	C/G	0.14	*-0.001* (0.008)	0.908	2070	0.11	0.006 (0.029)	0.845	515	0.08	0.02 (0.02)	0.24	1300
	rs11207426	1	A/G	0.38	*0.004* (0.005)	0.429	2070	0.31	*0.024* (0.021)	0.241	515	0.45	-0.01 (0.01)	0.53	1300
LVDD, cm	rs12541595	8	T/G	0.31	*-0.002* (0.008)	0.776	2069	0.23	0.032 (0.027)	0.225	785	0.07	0.02 (0.02)	0.44	1576
	rs10774625	12	G/A	0.52	*0.007* (0.008)	0.362	2069	0.70	*0.002* (0.025)	0.930	785	0.93	-0.001 (0.03)	0.96	1576
Mv-A	rs12440869	15	T/A	Not available				0.34	*-0.621* (1.164)	0.594	575	0.34	0.41 (0.94)	0.66	520

Betas in italics represent directional consistency with meta-analysis results; Bold results represent nominally significant findings ($P < 0.05$), results marked with * are significant after Bonferroni correction for 10 SNPS ($P < 0.005$)

[1] From Jackson Heart Study

[2] Northern Manhattan Study N = 97 for AoD and 194 for LVDD; Jackson Heart Study N = 1203 for AoD and 1382 for LVDD

AoD= diameter of the aortic root; LVDD= LV diastolic internal dimension; Chr= chromosome; EAF= effect allele frequency; SE= standard error

Table S9. Generalizability of novel findings for echocardiographic traits – Effect of genome-wide significant SNPs associated with aortic root diameter on pulse wave velocity in the AortaGen consortium

Trait	SNP	Effect / non-effect allele	Effect (SE)	*P*
Pulse wave velocity, m/s	rs806322	A/G	0.005 (0.012)	0.689
	rs6702619	G/T	0.003 (0.011)	0.805
	rs17696696	G/T	0.042 (0.011)	1.55×10^{-4}
	rs7127129	G/A	0.000 (0.011)	0.979
	rs17608766	C/T	-0.038 (0.016)	0.018
	rs4765663	C/G	0.007 (0.015)	0.630
	rs11207426	A/G	0.028 (0.012)	0.021

SE= standard error.

Table S10. Generalizability of novel findings for echocardiographic traits – Effect of genome-wide significant SNPs on incident heart failure HF and mortality in patients with HF the CHARGE – Heart Failure consortium

SNP	Effect/ non-effect allele	HR (95% CI) Incident HF	*P* Incident HF	HR (95% CI) Mortality in HF	*P* Mortality in HF
rs806322	A/G	0.97 (0.91-1.03)	0.306	1.00 (0.93-1.08)	0.971
rs6702619	G/T	0.99 (0.93-1.04)	0.636	1.02 (0.95-1.09)	0.635
rs17696696	G/T	1.00 (0.94-1.06)	0.950	1.06 (0.99-1.14)	0.103
rs7127129	G/A	0.99 (0.93-1.05)	0.705	1.00 (0.93-1.08)	0.941
rs17608766	C/T	1.11 (1.01-1.21)	0.033	0.98 (0.87-1.11)	0.799
rs4765663	C/G	1.04 (0.97-1.12)	0.254	1.01 (0.92-1.10)	0.907
rs11207426	A/G	1.07 (1.01-1.14)	0.027	1.04 (0.97-1.12)	0.289
rs12541595	T/G	0.96 (0.90-1.03)	0.232	1.00 (0.92-1.08)	0.999
rs10774625	G/A	1.00 (0.95-1.06)	0.963	1.01 (0.94-1.09)	0.726
rs12440869	T/A	1.04 (0.97-1.11)	0.263	0.93 (0.86-1.00)	0.062

HR= hazard ratio; CI= confidence interval; HF= heart failure.

Table S11. Generalizability of novel findings for echocardiographic traits – Effect of the novel genome-wide significant SNPs on all-cause, cardiovascular and heart failure mortality in the LURIC cohort of patients with suspected coronary artery disease

SNP	Effect/ non-effect allele	HR (95% CI) Mortality	*P* Mortality	HR (95% CI) CV mortality	*P* CV mortality	HR (95% CI) HF mortality	*P* HF mortality
rs806322	A/G	1.09 (0.99-1.20)	0.079	1.05 (0.93-1.19)	0.428	0.83 (0.65-1.07)	0.145
rs6702619	G/T	1.01 (0.92-1.11)	0.806	0.99 (0.88-1.11)	0.827	0.87 (0.68-1.12)	0.279
rs17696696	G/T	0.93 (0.85-1.03)	0.146	0.96 (0.85-1.08)	0.451	0.94 (0.74-1.21)	0.642
rs7127129	G/A	0.95 (0.86-1.04)	0.275	0.97 (0.86-1.09)	0.600	0.85 (0.66-1.09)	0.205
rs17608766	C/T	0.98 (0.86-1.12)	0.758	0.97 (0.82-1.15)	0.717	0.92 (0.64-1.31)	0.638
rs4765663	C/G	1.01 (0.89-1.14)	0.875	0.95 (0.81-1.11)	0.517	1.07 (0.77-1.47)	0.701
rs11207426	A/G	1.08 (0.98-1.19)	0.109	1.05 (0.93-1.19)	0.399	1.43 (1.13-1.83)	4.0×10^{-3}
rs12541595	T/G	0.99 (0.89-1.09)	0.788	0.97 (0.85-1.10)	0.615	0.96 (0.74-1.26)	0.784
rs10774625	G/A	0.95 (0.86-1-04)	0.238	0.94 (0.83-1.05)	0.273	0.89 (0.70-1.14)	0.368
rs12440869	T/A	0.97 (0.87-1.08)	0.546	0.90 (0.78-1.03)	0.131	0.95 (0.71-1.26)	0.710

HR= hazard ratio; CI= confidence interval; CV= cardiovascular; HF= heart failure.

Table S12. Generalizability of novel findings for echocardiographic traits – Effect of the novel genome-wide significant SNPs on myocardial infarction (MI) and coronary artery disease (CAD) in the CARDIOGRAMplusC4D Consortium

SNP	Effect/ non-effect allele	HR (95% CI) MI	*P* MI	HR (95% CI) CAD	*P* CAD
rs806322	A/G	1.00 (0.98-1.02)	0.696	1.00 (0.98-1.02)	0.912
rs6702619	G/T	0.99 (0.97-1.01)	0.288	1.00 (0.98-1.02)	0.960
rs17696696	G/T	1.03 (1.00-1.05)	0.021	1.04 (1.02-1.06)	8.45×10^{-6}
rs7127129	G/A	1.02 (1.00-1.05)	0.023	1.02 (1.00-1.03)	0.113
rs17608766	C/T	1.05 (1.02-1.09)	0.002	1.05(1.02-1.09)	4.94×10^{-4}
rs4765663	C/G	0.99 (0.96-1.01)	0.323	0.99 (0.97-1.02)	0.551
rs11207426	A/G	0.99 (0.97-1.01)	0.218	0.98 (0.96-0.99)	0.011
rs12541595	T/G	1.00 (0.98-1.03)	0.736	1.00 (0.99-1.03)	0.636
rs10774625	G/A	0.93 (0.91-0.95)	5.09×10^{-11}	0.94 (0.92-0.96)	2.69×10^{-10}
rs12440869	T/A	1.00 (0.98-1.03)	0.688	1.00 (0.98-1.02)	0.799

HR= hazard ratio; CI= confidence interval; MI= myocardial infarction; CAD = coronary artery disease.

Table S 13: Top canonical pathways enriched with echo-related genes from Ingenuity Pathway Analysis

Ingenuity Canonical Pathways	*P* value	FDR	Ratio	Genes
Protein Kinase A Signaling	5.8×10^{-6}	0.002	19/386	*ADCY8, CAMK2B, CDC27, CREB5, DUSP12, DUSP18, FLNC, GLI3, GNB4, HIST2H3C, LEF1, MYL4, NFKBIA, OPN1SW, PLCE1, PLCG1, PLN, PRKCA, TTN*
Death Receptor Signaling	6.9×10^{-5}	0.012	8/92	*ACTA2, ART1, CRADD, FADD, FAS, LIMK1, NFKBIA, TNFRSF1A*
Wnt/Ca+ pathway	2.2×10^{-4}	0.019	6/56	*AXIN1, CREB5, DVL1, PLCE1, PLCG1, PRKCA*
P2Y Purigenic Receptor Signaling	4.1×10^{-4}	0.028	8/119	*ADCY8, CREB5, GNB4, ITGB3, OPN1SW, PLCE1, PLCG1, PRKCA*

FDR: False discovery rate; Ratio: number of molecules in a given pathway that meet cut criteria, divided by total number of molecules that make up that pathway

Table S 14: Top canonical pathways enriched with echo-related genes from Ingenuity Pathway Analysis: additional informations on gene loci

Gene	Length	Most significant SNP within gene region	Locus
ACTA2	56317	rs2862834	10q23.31
ADCY8	260289	rs263255	8q24.22
ART1	19286	rs7103680	11p15.4
AXIN1	65237	rs2685127	16p13.3
CAMK2B	108482	rs7804804	7p13
CDC27	71355	rs2292864	17q21.32
CRADD	173381	rs10859579	12q22
CREB5	526572	rs917275	7p15.1
DUSP12	7372	rs953301	1q23.3
DUSP18	5834	rs734479	22q12.2
DVL1	13835	rs12142199	1p36.33
FADD	4240	rs7127129	11q13.3
FAS	25255	rs2862834	10q23.31
FLNC	28846	rs7786074	7q32.1
GLI3	276071	rs7782675	7p14.1
GNB4	55496	rs4855074	3q26.33
HIST2H3C	507	rs532941	1q21.2
ITGB3	58870	rs2292864	17q21.32
LEF1	121412	rs7665502	4q25
LIMK1	38749	rs4717863	7q11.23
MYL4	14618	rs3892085	17q21.32
NFKBIA	3245	rs8019505	14q13.2
OPN1SW	3302	rs7786074	7q32.1
PLCE1	239319	rs3758524	10q23.33
PLCG1	38197	rs2866372	20q12
PLN	12146	rs11967375	6q22.31
PRKCA	507937	rs6504434	17q24.2
TNFRSF1A	13361	rs7958488	12p13.31
TTN	281432	rs12052983	2q31.2

Table S 15: DEPICT

Results of the DEPICT analyses are summarized in the Supplemental Excel file "Supplemental Table 15.xlsx"

Table S 16: Cis eQTL analyses of whole blood and monocytic gene expression data

SNP	Chr	Effect Allele	Illumina_ID	Gene Name	*P* value WESTRA Whole Blood	*P* value GHS Monocytes
rs10774625	12	A	ILMN_1743829	*ATXN2*	(-) 2.3 x 10^{-3}	NS
			ILMN_1752046	***SH2B3***	(+) 8.2 x 10^{-20}	(+) 1.8 x 10^{-4}
rs12440869	15	T	ILMN_1655311	*C15orf61*	(+) 7.2 x 10^{-7}	NS
			ILMN_1682738	*SMAD3*	(-) 8.2 x 10^{-13}	NS
rs17608766	17	C	ILMN_1815495	*LOC644391*	(+) 1.3 x 10^{-9}	NS
			ILMN_1722812	*GOSR2*	(-) 6.4 x 10^{-6}	NS
			ILMN_1656293	*GOSR2*	(+) 2.0 x 10^{-3}	NS
			ILMN_1680353	*NSF*	(+) 2.3 x 10^{-4}	NS
rs17696696	16	T	ILMN_1657139	*ADAT1*	(+) 5.7 x 10^{-6}	NS
			ILMN_1800837	***CFDP1***	(+) 6.2 x 10^{-11}	(+) 7.6 x 10^{-5}
rs2649	15	T	ILMN_1786211	*HERC1*	(+) 1.6 x 10^{-3}	NS
rs7127129	11	G	ILMN_1758658	***FADD***	(+) 1.6 x 10^{-37}	(+) 2.7 x 10^{-4}
rs806322	13	G	ILMN_2043918	*DLEU1*	(+) 1.4 x 10^{-5}	NS
rs11153730	6	C	ILMN_1904851	*C6orf204*	(+) 8.36 x 10^{-22}	NS
			ILMN_2270100	*C6orf204*	(+) 3.01 x 10^{-05}	NS
			ILMN_1855286	*CEP85L*	(+) 3.46 x 10^{-04}	NS
rs1532292	17	T	ILMN_1753515	***SRR***	(-) 3.40 x 10^{-20}	(-) 4.63 x 10^{-10}

Results from the eQTL analysis of SNPs identified in GWAS meta-analysis. Cis was defined as 250kb upstream/downstream of the respective SNP. (+) /(-) specify the effect directions of the eQTL with respect to the Effect Allele. A significance threshold of 0.01/15 ($p=6.6 \times 10^{-4}$) was used to adjust for multiple testing.

Table S 17: Significant eQTLs in the Genotype-Tissue Expression (GTEx) database

SNP ID	Gencode ID	Gene Symbol	Effect allele	*P* value	Effect size	Tissue
rs17696696	ENSG00000261783.1	*RP11-252K23.2*	G	2.00E-23	-0.77	Cells - Transformed fibroblasts
rs17696696	ENSG00000261783.1	*RP11-252K23.2*	G	2.50E-22	-0.69	Thyroid
rs17696696	ENSG00000261783.1	*RP11-252K23.2*	G	1.70E-20	-0.87	Adipose - Visceral (Omentum)
rs17696696	ENSG00000153774.4	*CFDP1*	G	6.20E-17	-0.34	Cells - Transformed fibroblasts
rs17696696	ENSG00000050820.12	*BCAR1*	G	8.40E-17	-0.48	Esophagus - Mucosa
rs17696696	ENSG00000261783.1	*RP11-252K23.2*	G	3.10E-16	-0.72	Artery - Aorta
rs17696696	ENSG00000261783.1	*RP11-252K23.2*	G	8.80E-16	-0.63	Esophagus - Mucosa
rs17696696	ENSG00000261783.1	*RP11-252K23.2*	G	1.60E-15	-0.59	Lung
rs17696696	ENSG00000261783.1	*RP11-252K23.2*	G	5.70E-15	-0.58	Artery - Tibial
rs17696696	ENSG00000261783.1	*RP11-252K23.2*	G	6.80E-15	-0.58	Nerve - Tibial
rs17696696	ENSG00000261783.1	*RP11-252K23.2*	G	2.70E-14	-0.52	Adipose - Subcutaneous
rs17696696	ENSG00000261783.1	*RP11-252K23.2*	G	1.60E-10	-0.58	Esophagus - Muscularis
rs17696696	ENSG00000050820.12	*BCAR1*	G	1.70E-10	0.26	Artery - Aorta
rs17696696	ENSG00000261783.1	*RP11-252K23.2*	G	6.90E-10	-0.69	Adrenal Gland
rs17696696	ENSG00000050820.12	*BCAR1*	G	7.30E-10	0.19	Artery - Tibial
rs17696696	ENSG00000261783.1	*RP11-252K23.2*	G	1.30E-09	-0.72	Pancreas
rs17696696	ENSG00000261783.1	*RP11-252K23.2*	G	1.30E-09	-0.45	Skin - Sun Exposed (Lower leg)
rs17696696	ENSG00000261783.1	*RP11-252K23.2*	G	2.00E-09	-0.56	Breast - Mammary Tissue
rs17696696	ENSG00000261783.1	*RP11-252K23.2*	G	1.50E-08	-0.43	Whole Blood
rs17696696	ENSG00000261783.1	*RP11-252K23.2*	G	1.60E-08	-0.62	Artery - Coronary
rs17696696	ENSG00000153774.4	*CFDP1*	G	1.10E-07	-0.19	Adipose - Subcutaneous
rs17696696	ENSG00000261783.1	*RP11-252K23.2*	G	2.50E-07	-0.63	Vagina
rs17696696	ENSG00000261783.1	*RP11-252K23.2*	G	3.00E-07	-0.63	Colon - Sigmoid
rs17696696	ENSG00000261783.1	*RP11-252K23.2*	G	5.10E-07	-0.72	Brain - Cerebellar Hemisphere
rs17696696	ENSG00000261783.1	*RP11-252K23.2*	G	5.30E-07	-0.64	Prostate
rs17696696	ENSG00000166822.8	*TMEM170A*	G	6.30E-07	0.23	Skin - Sun Exposed (Lower leg)
rs17696696	ENSG00000261783.1	*RP11-252K23.2*	G	1.40E-06	-0.53	Stomach
rs17696696	ENSG00000153774.4	*CFDP1*	G	1.70E-06	-0.17	Skin - Sun Exposed (Lower leg)
rs17696696	ENSG00000153774.4	*CFDP1*	G	1.80E-06	-0.41	Brain - Hippocampus
rs17696696	ENSG00000166822.8	*TMEM170A*	G	2.00E-06	-0.21	Nerve - Tibial
rs17696696	ENSG00000261783.1	*RP11-252K23.2*	G	4.00E-06	-0.47	Colon - Transverse
rs17696696	ENSG00000153774.4	*CFDP1*	G	6.10E-06	-0.17	Nerve - Tibial
rs7127129	ENSG00000254721.1	*RP11-805J14.5*	G	5.40E-10	0.23	Cells - Transformed fibroblasts
rs7127129	ENSG00000168040.4	*FADD*	G	2.10E-09	0.22	Cells - Transformed fibroblasts
rs17608766	ENSG00000179673.3	*RPRML*	C	1.60E-10	-0.56	Muscle - Skeletal
rs17608766	ENSG00000179673.3	*RPRML*	C	3.00E-05	-0.44	Adipose - Subcutaneous
rs11207426	ENSG00000224609.2	*RP11-470E16.1*	A	7.20E-21	0.68	Artery - Tibial
rs11207426	ENSG00000224609.2	*RP11-470E16.1*	A	8.00E-16	0.49	Adipose - Subcutaneous
rs11207426	ENSG00000224609.2	*RP11-470E16.1*	A	4.20E-15	0.62	Artery - Aorta
rs11207426	ENSG00000224609.2	*RP11-470E16.1*	A	7.90E-15	0.56	Nerve - Tibial
rs11207426	ENSG00000224609.2	*RP11-470E16.1*	A	6.70E-12	0.5	Skin - Sun Exposed (Lower leg)
rs11207426	ENSG00000224609.2	*RP11-470E16.1*	A	8.90E-08	0.53	Artery - Coronary
rs11207426	ENSG00000224609.2	*RP11-470E16.1*	A	1.50E-07	-0.23	Muscle - Skeletal
rs11207426	ENSG00000224609.2	*RP11-470E16.1*	A	2.00E-07	0.51	Skin - Not Sun Exposed (Suprapubic)
rs11207426	ENSG00000224609.2	*RP11-470E16.1*	A	2.20E-07	0.43	Breast - Mammary Tissue
rs12541595	ENSG00000170873.14	*MTSS1*	T	7.00E-18	-0.61	Heart - Left Ventricle
rs12541595	ENSG00000249816.2	*LINC00964*	T	7.00E-11	-0.53	Heart - Left Ventricle
rs10774625	ENSG00000111275.8	*ALDH2*	G	1.00E-08	-0.26	Skin - Sun Exposed (Lower leg)
rs12440869	ENSG00000103591.8	*AAGAB*	T	1.30E-06	-0.19	Esophagus - Muscularis
rs1532292	ENSG00000236838.2	*AC090617.1*	G	3.50E-11	0.78	Testis
rs1532292	ENSG00000167720.8	*SRR*	G	2.50E-10	0.33	Cells - Transformed fibroblasts
rs1532292	ENSG00000167720.8	*SRR*	G	7.70E-10	0.38	Adipose - Subcutaneous
rs1532292	ENSG00000141258.8	*SGSM2*	G	7.20E-09	-0.21	Esophagus - Mucosa
rs1532292	ENSG00000167720.8	*SRR*	G	8.00E-09	0.42	Adrenal Gland

rs1532292	ENSG00000167720.8	*SRR*	G	1.00E-08	0.37	Artery - Tibial
rs1532292	ENSG00000167720.8	*SRR*	G	1.10E-08	0.41	Esophagus - Mucosa
rs1532292	ENSG00000167720.8	*SRR*	G	1.70E-08	0.34	Lung
rs1532292	ENSG00000167720.8	*SRR*	G	3.30E-07	0.38	Breast - Mammary Tissue
rs1532292	ENSG00000167720.8	*SRR*	G	3.60E-07	0.38	Colon - Transverse
rs1532292	ENSG00000167720.8	*SRR*	G	7.90E-07	0.3	Esophagus - Muscularis
rs1532292	ENSG00000167720.8	*SRR*	G	1.40E-06	0.42	Stomach
rs1532292	ENSG00000141258.8	*SGSM2*	G	1.70E-06	-0.22	Skin - Sun Exposed (Lower leg)
rs1532292	ENSG00000167720.8	*SRR*	G	1.70E-06	0.34	Artery - Aorta
rs1532292	ENSG00000141258.8	*SGSM2*	G	3.80E-06	-0.23	Skin - Not Sun Exposed (Suprapubic)
rs1532292	ENSG00000167720.8	*SRR*	G	4.00E-06	0.31	Thyroid
rs1532292	ENSG00000263345.1	*RP1-59D14.5*	G	1.10E-05	-0.22	Skin - Sun Exposed (Lower leg)
rs11153730	ENSG00000217330.1	*SSXP10*	C	1.10E-10	0.36	Artery - Tibial
rs11153730	ENSG00000217330.1	*SSXP10*	C	9.70E-07	0.39	Artery - Aorta
rs11153730	ENSG00000217330.1	*SSXP10*	C	6.40E-06	0.48	Heart - Atrial Appendage

This searches our precalculated eQTLs as generated by Matrix eQTL for tissues having more than 70 samples, using a +/- 1 Mb cis window around the transcript start site (TSS). These results have been filtered using a q-value threshold. More details are presented on the documentation page (Analysis Methods). URL: http://gtexportal.org/home/

Table S 88: Percentage of variance explained by the genome-wide significant SNPs per phenotype in the Rotterdam Study, the Study of Health in Pomerania and the Framingham Heart Study

Trait	RS-I (%)	RS-II (%)	RS-III (%)	SHIP (%)	FHS (%)	Sample-size weighted mean (%)	Sample-size weighted mean – novel SNPs only (%)
AoD	2.7	3.0	2.2	1.0	1.2	1.7	1.0
LVDD	0.2	0.4	0.3	0.5	0.7	0.5	0.3
Mv-A	0.4	4.0×10^{-4}	0.2	0.2	0.4	0.2	NA

Table S 19: Explained variance of all autosomal SNPs (MAF ≥ 1%) in SHIP

Trait	Explained Variance (%)	SE (%)	*P* value	N
AoD	29	8.2	1.1×10^{-4}	3,458
LA	16	8.3	2.1×10^{-2}	3,457
LVDD	18	9.0	1.9×10^{-2}	3,168
LVWT	18	8.9	1.4×10^{-2}	3,168
LVM	12	8.5	0.07	3,168
FS	17	9.1	2.3×10^{-2}	3,116
LVSD	8.2	9.3	0.19	3,120
Mv-A	11	12.2	0.18	2,315
DecTime	16	11.9	0.09	2,364
IVRT	24	12.2	1.9×10^{-2}	2,303
HFpEF	20	16.6	0.13	1,766

AoD= aortic root diameter; LA= left atrial size; LVDD= left ventricular end-diastolic diameter; LVWT= left ventricular wall thickness; LVM= left ventricular mass; FS= left ventricular fractional shortening; LVSD= left ventricular systolic dysfunction; A= peak velocity of the mitral A-wave; DecTime= deceleration time; IVRT= isovolumetric relaxation time; HFpEF= heart failure with preserved ejection fraction; SE= standard error; * P values are from GCTA analyses.[11] The explained variance for the traits E (peak velocity of the mitral E-wave), E/A (ratio of the peak velocity of the mitral E-Wave divided by the peak velocity of the mitral A-wave) and DDpEF (diastolic dysfunction with preserved ejection fraction) was 0 – therefore the numbers are not displayed in this table. For the traits E´ (Peak velocity of the excursion of the lateral mitral annulus in the early diastolic phase) and E/E´ (Ratio of the peak velocity of the excursion of the lateral mitral annulus in the early diastolic phase by TDI and the peak velocity of the mitral E-wave by Doppler imaging) no values were calculated due to the low number of samples available in SHIP.

Figure S 1: QQ plot - AoD.

P values were obtained by calculating Wald test statistics (sample size: n=26,741).

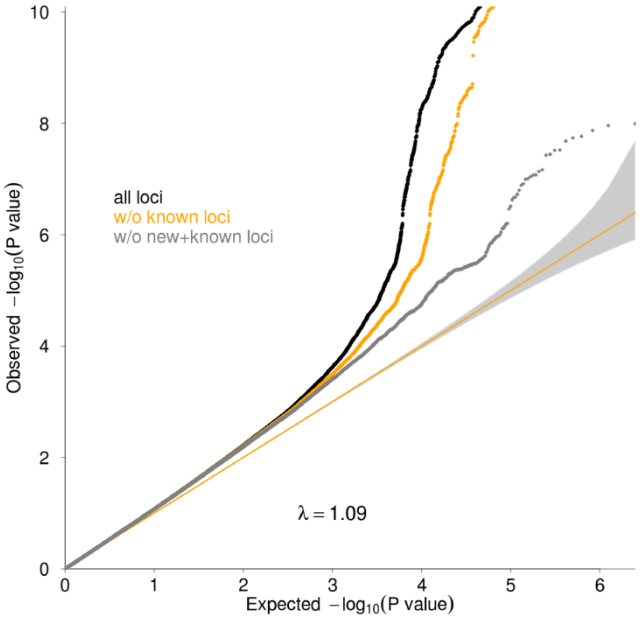


Figure S 2: QQ plot – LA.

P values were obtained by calculating Wald test statistics (sample size: n=26,189).

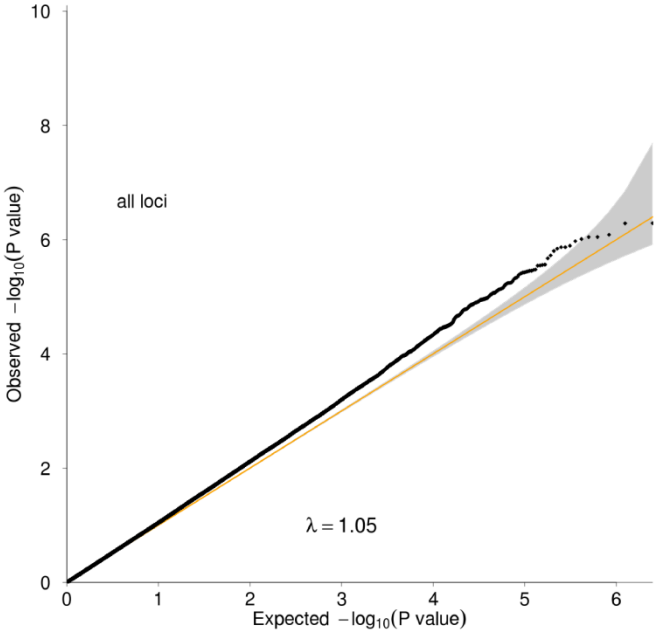


Figure S 3: QQ plot – LVDD.

P values were obtained by calculating Wald test statistics (sample size: n=30,201).

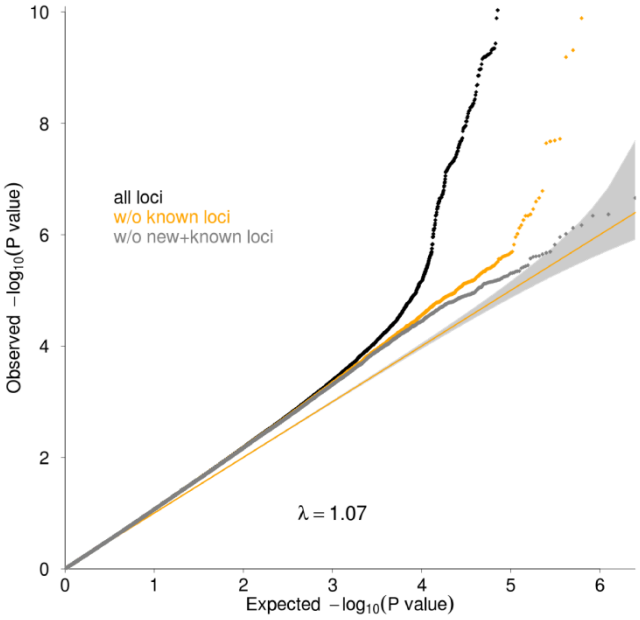


Figure S 4: QQ plot – LVWT.

P values were obtained by calculating Wald test statistics (sample size: n=30,043).

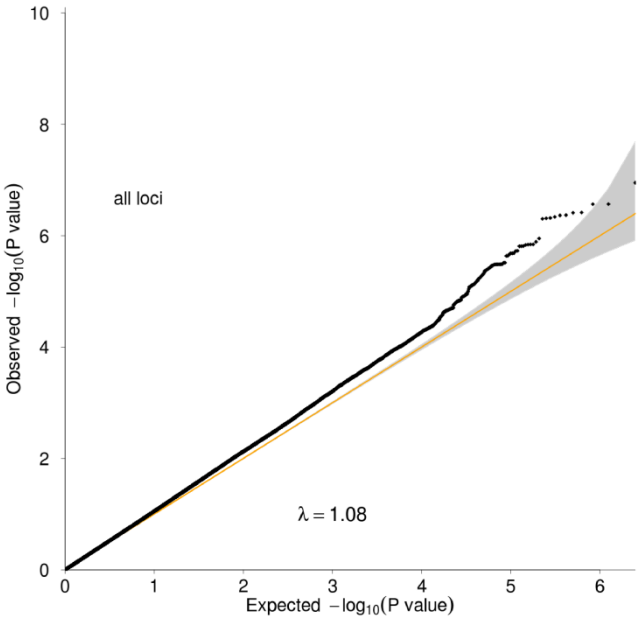


Figure S 5: QQ plot – LVM.

P values were obtained by calculating Wald test statistics (sample size: n=30,142).

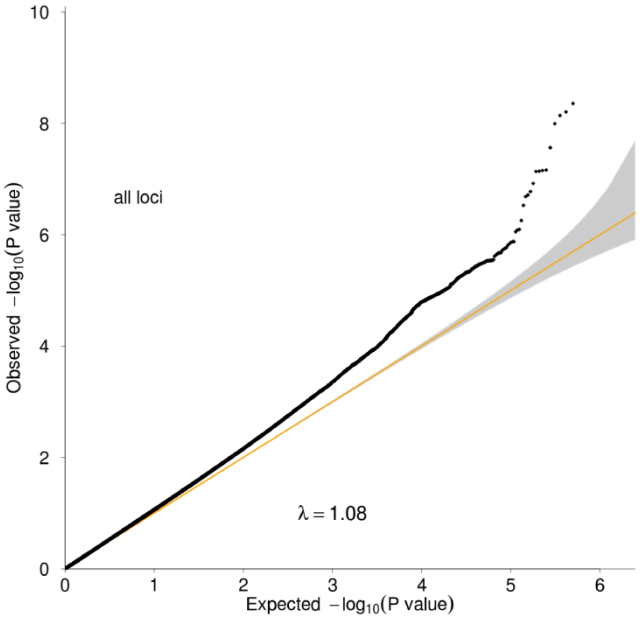


Figure S 6: QQ plot – FS.

P values were obtained by calculating Wald test statistics (sample size: n=28,083).

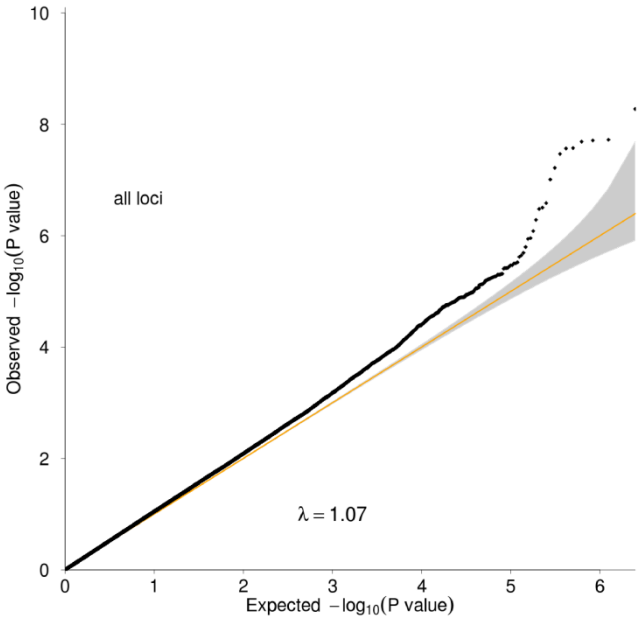


Figure S 7: LVSD.

P values were obtained by calculating Wald test (sample size: n=27,864).

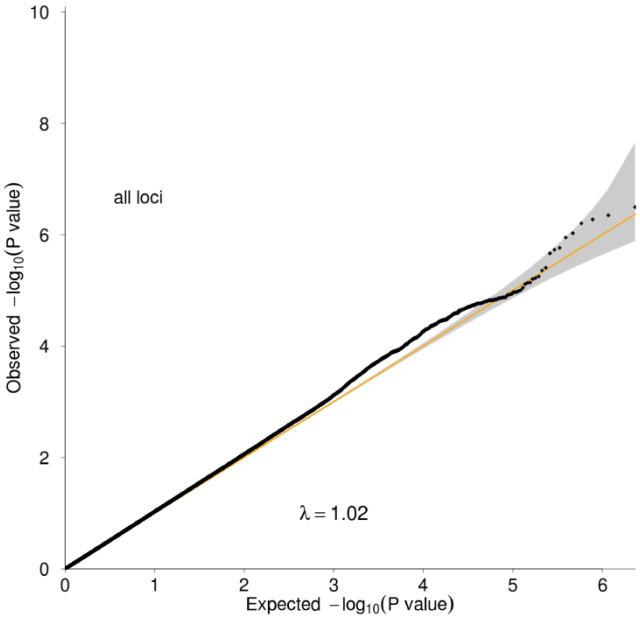


Figure S 8: QQ plot Mv-E.

P values were obtained by calculating Wald test (sample size: n=21,852).

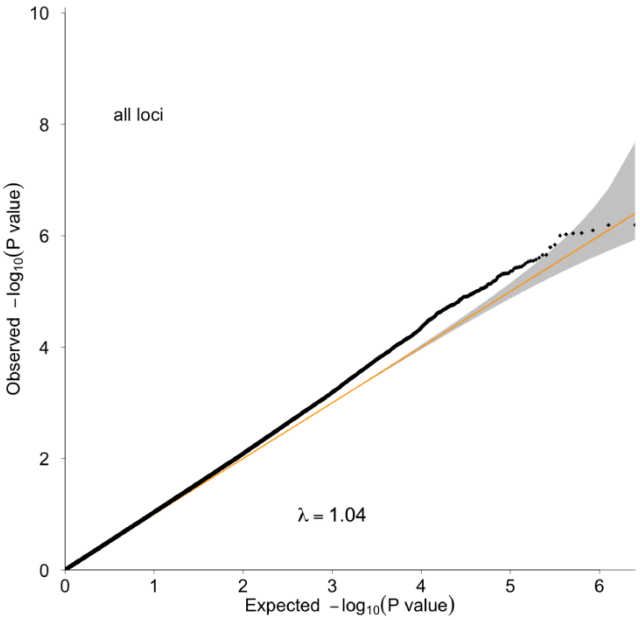


Figure S 9: QQ plot – Mv-A.

P values were obtained by calculating Wald test statistics (sample size: n=21,643).

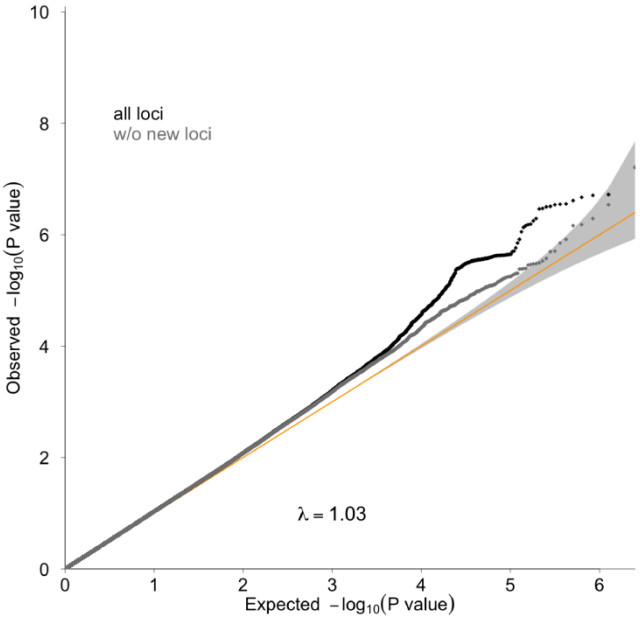


Figure S 10: QQ plot – E/A.

P values were obtained by calculating Wald test statistics (sample size: n=21,348).

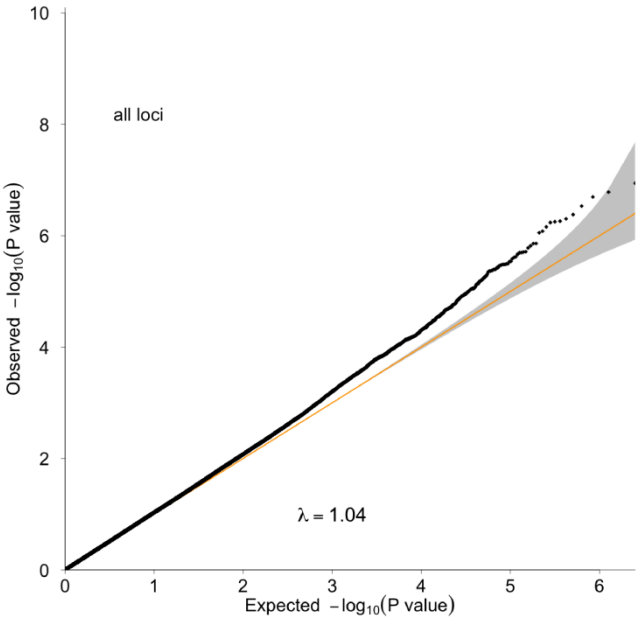


Figure S 11: QQ plot – DecTime.

P values were obtained by calculating Wald test statistics (sample size: n=16,681).

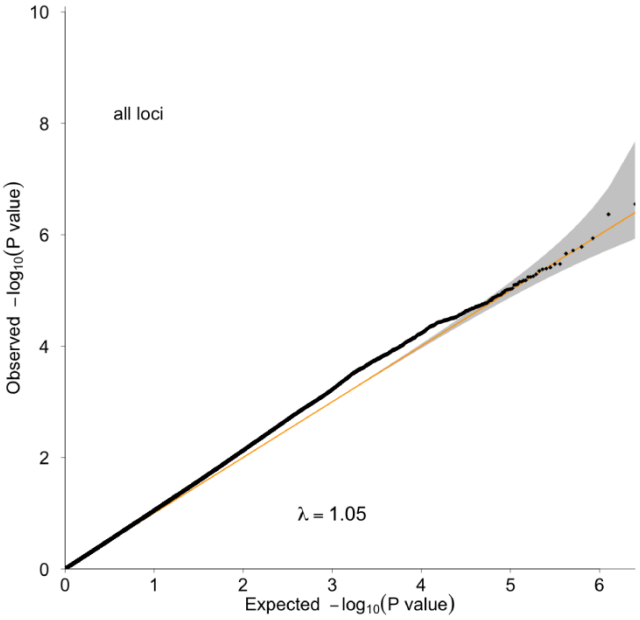


Figure S 12: QQ plot – IVRT.

P values were obtained by calculating Wald test statistics (sample size: n=12,151).

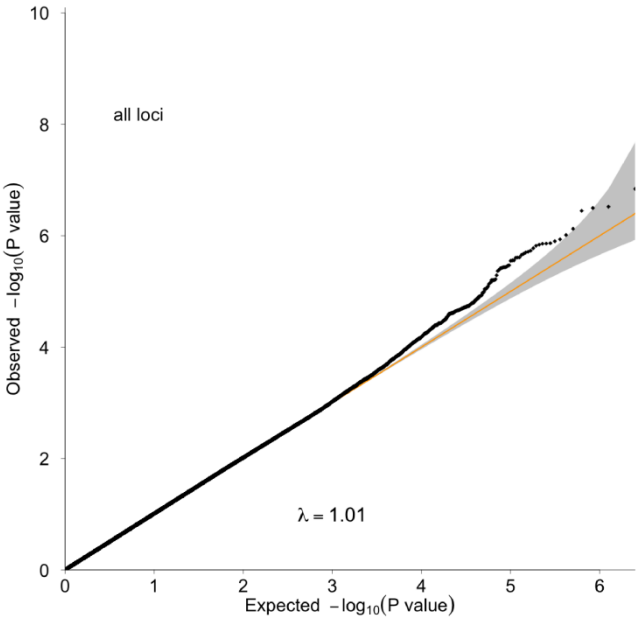


Figure S 13: QQ plot – E'.

P values were obtained by calculating Wald test statistics (sample size: n=8,500).

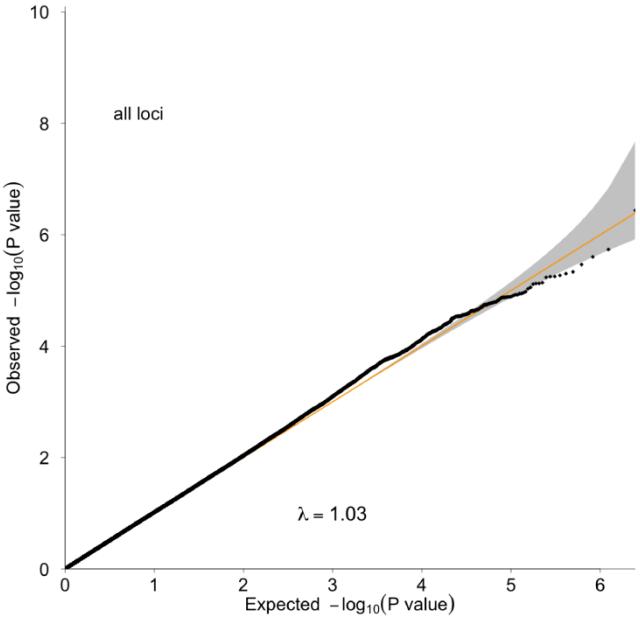


Figure S 14: QQ plot – E/E'.

P values were obtained by calculating Wald test statistics (sample size: n=7,832).

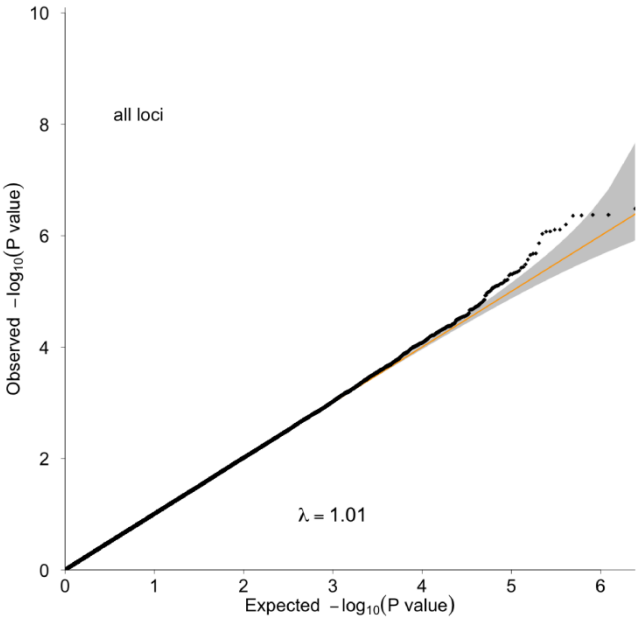


Figure S 15: QQ plot – DDpEF.

P values were obtained by calculating Wald test statistics (sample size: n=7,262).

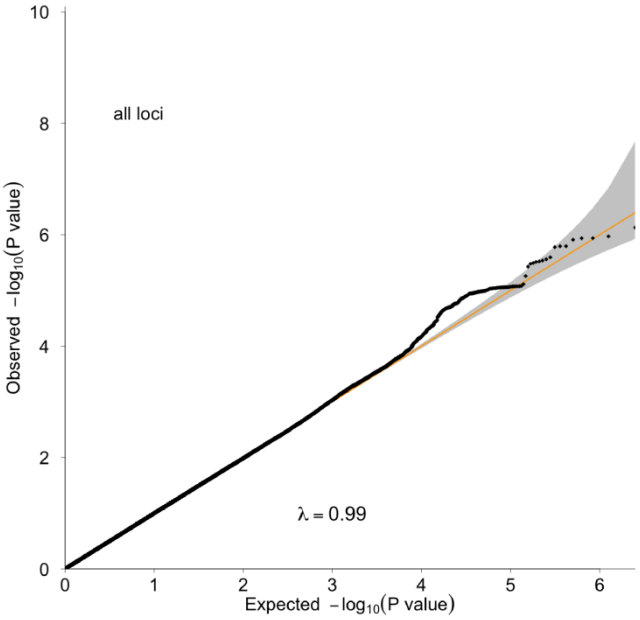


Figure S 16: QQ plot – HFpEF.

P values were obtained by calculating Wald test statistics (sample size: n=5,297).

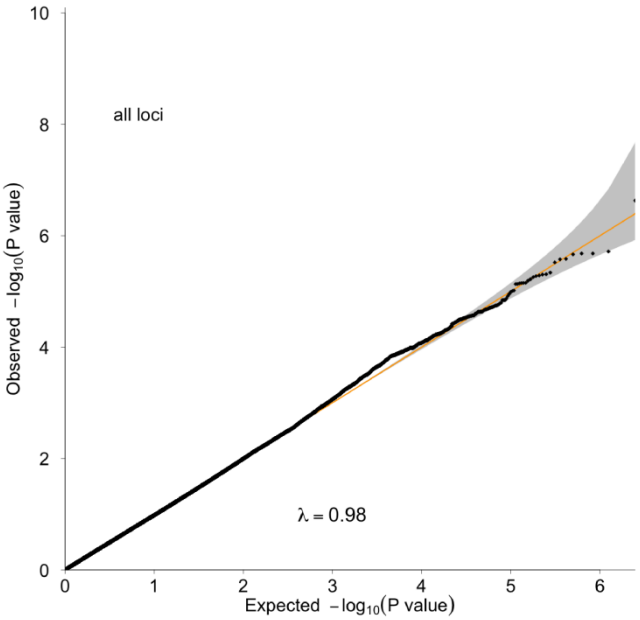
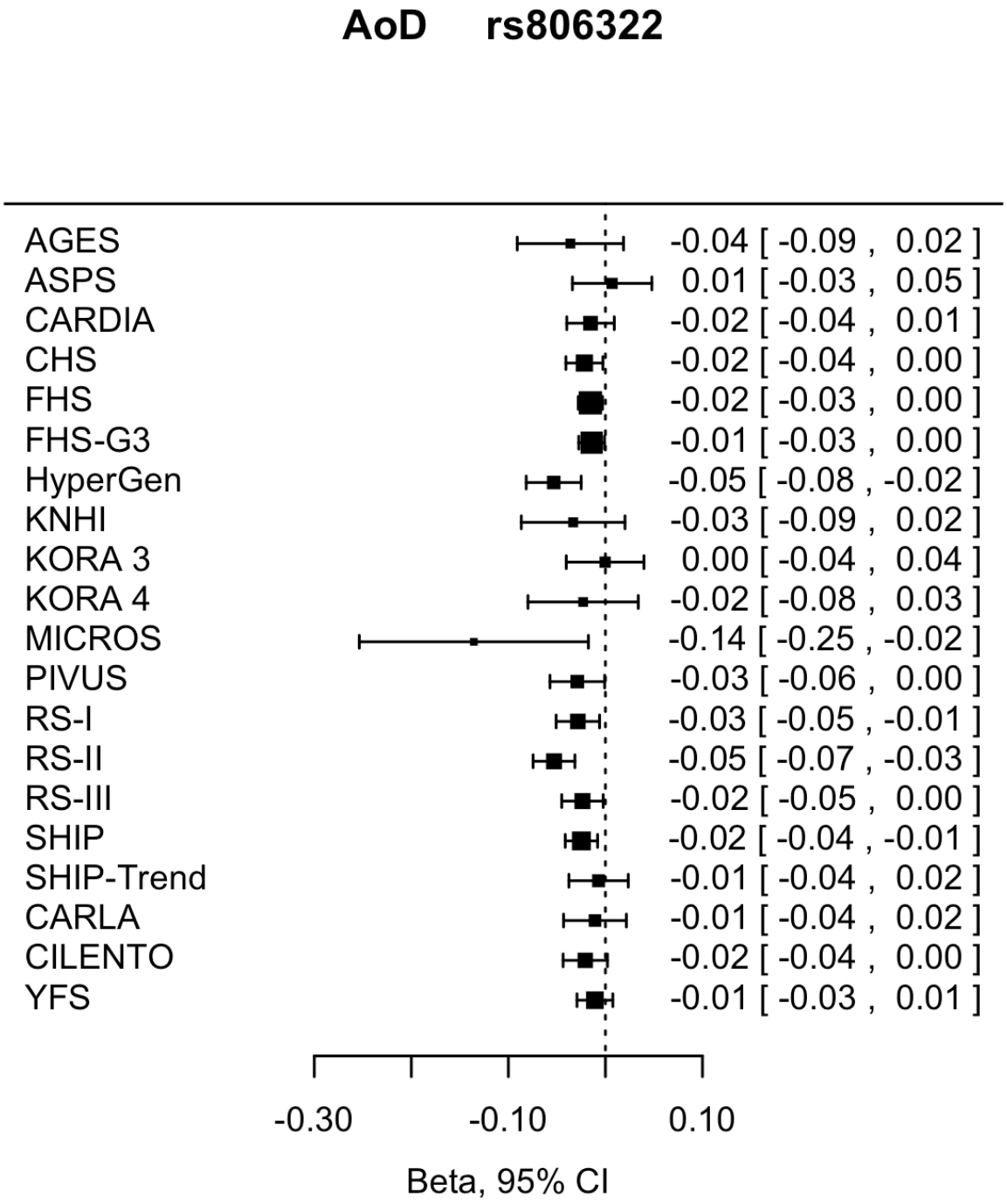
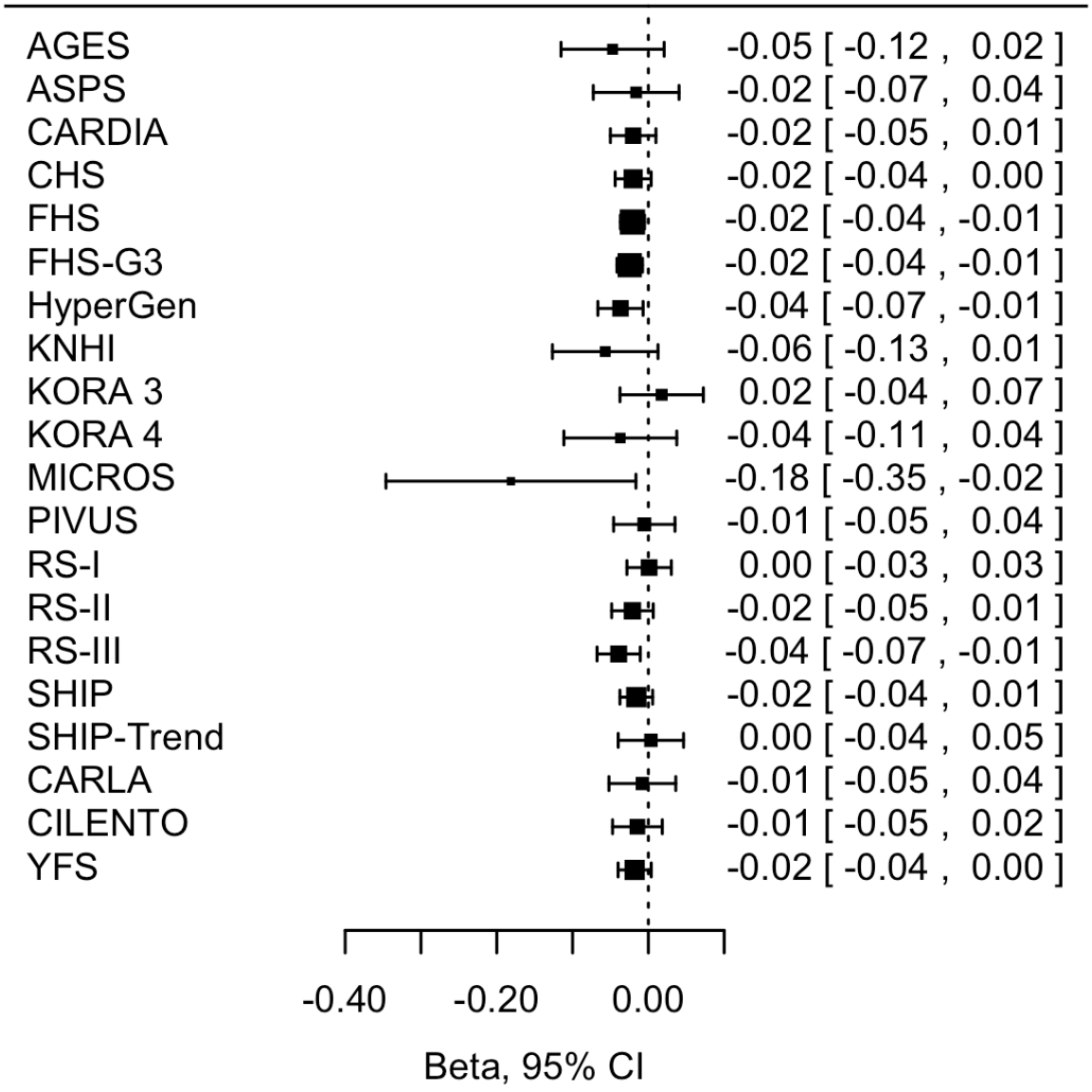


Figure S 17: Forest plots for genome-wide significant hits



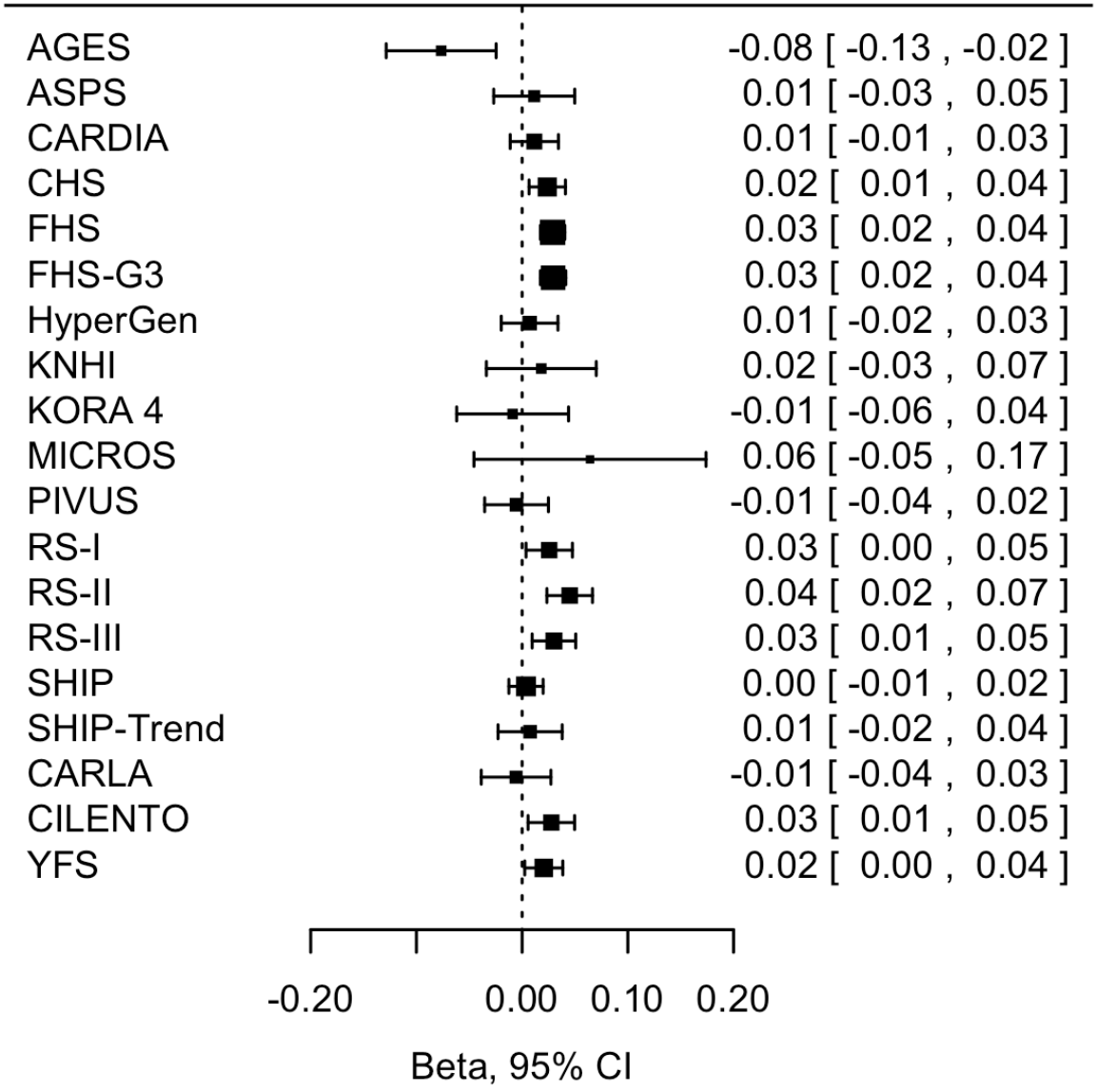
n=30,704

AoD rs4765663



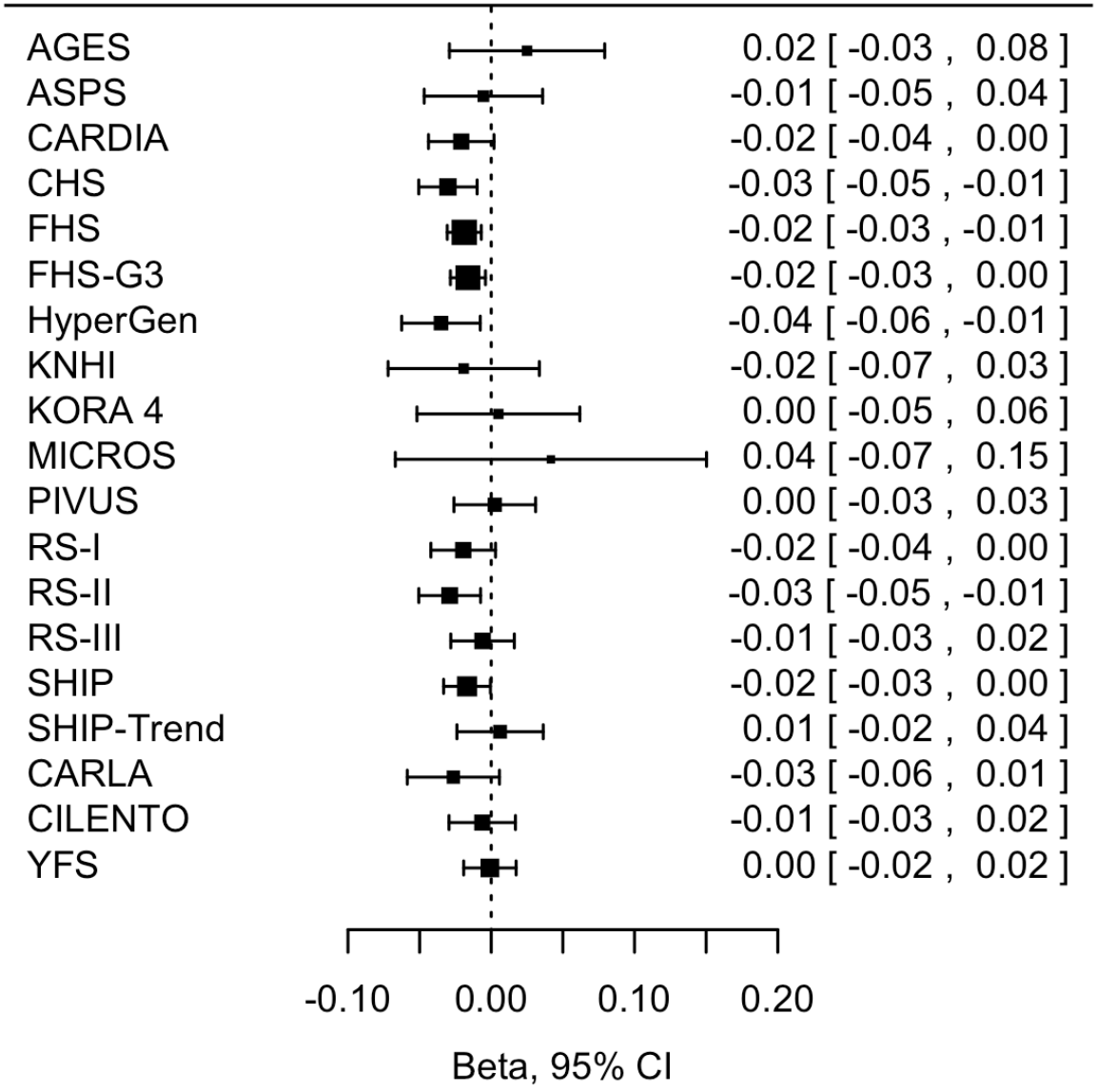
n=30,704

AoD rs6702619



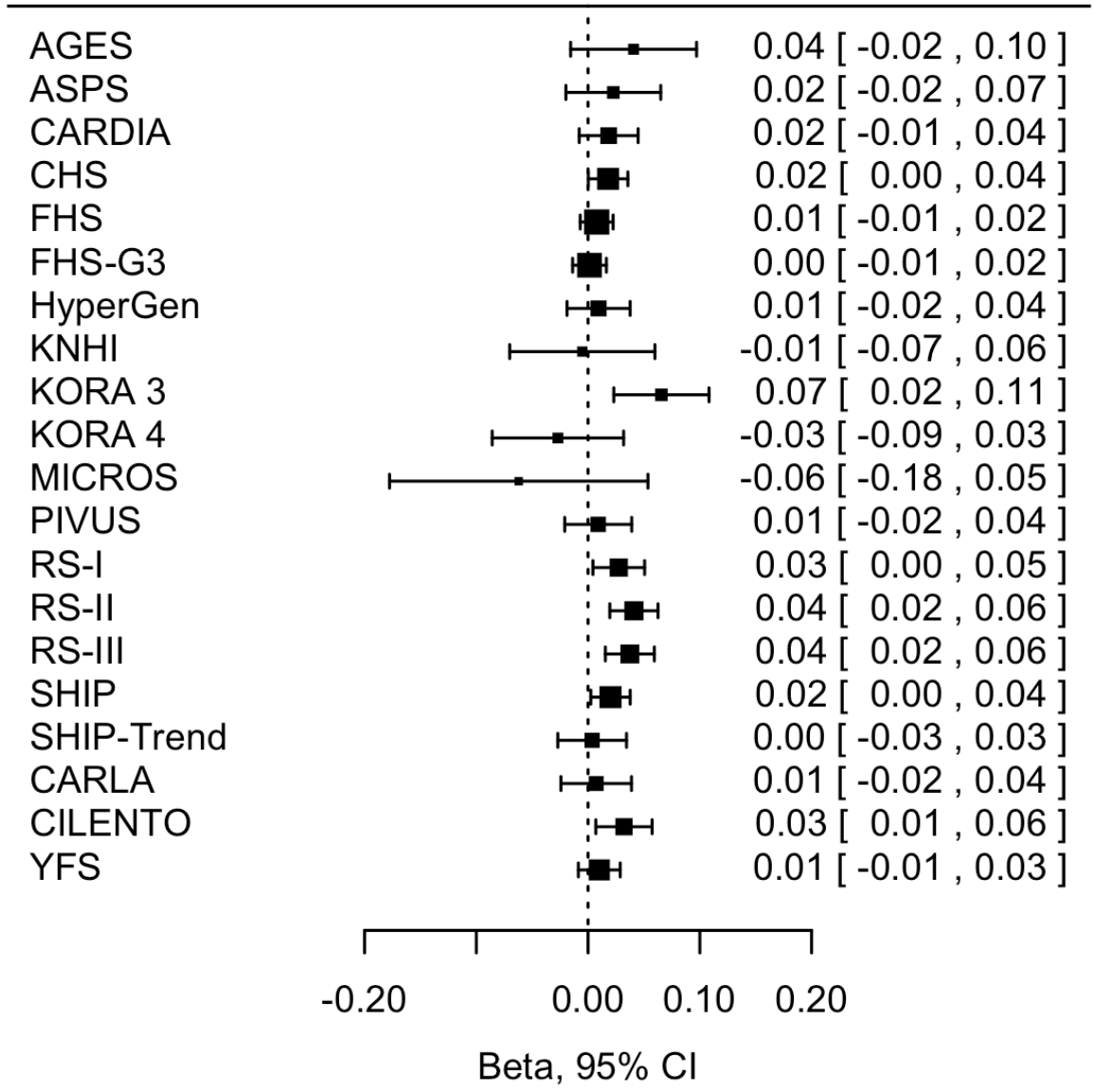
n=30,704

AoD rs7127129



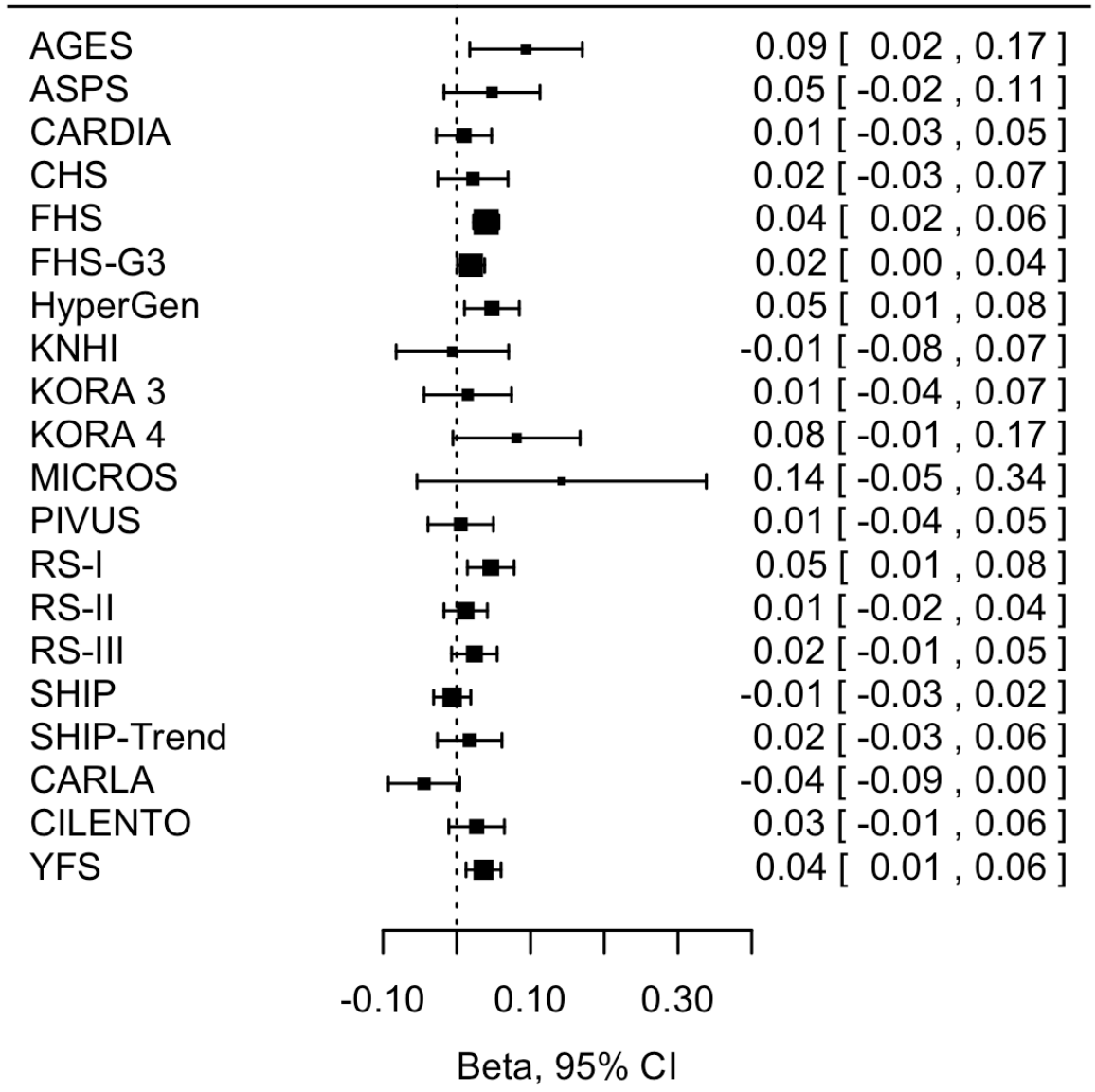
n=30,704

AoD rs11207426



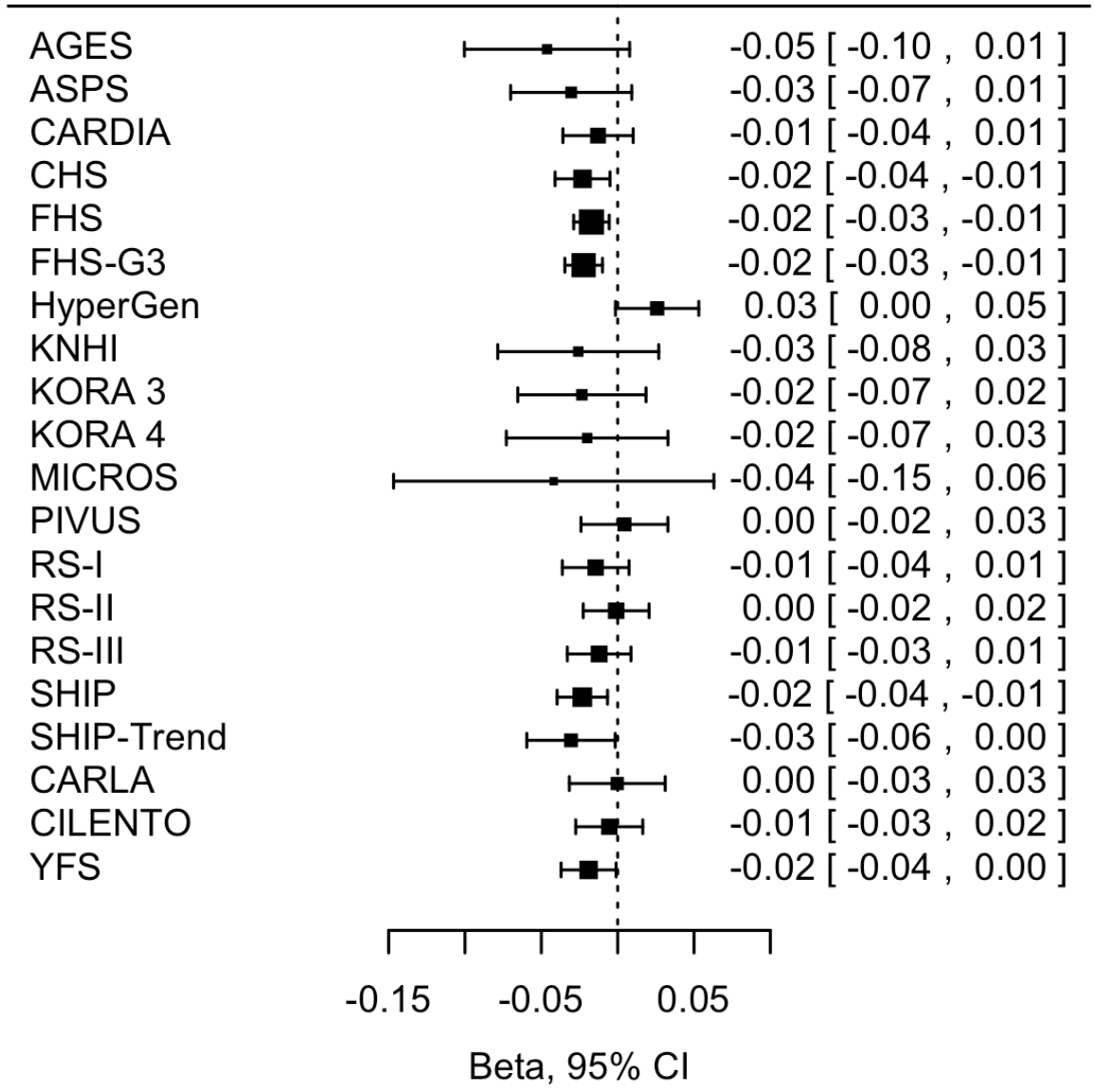
n=30,704

AoD rs17608766



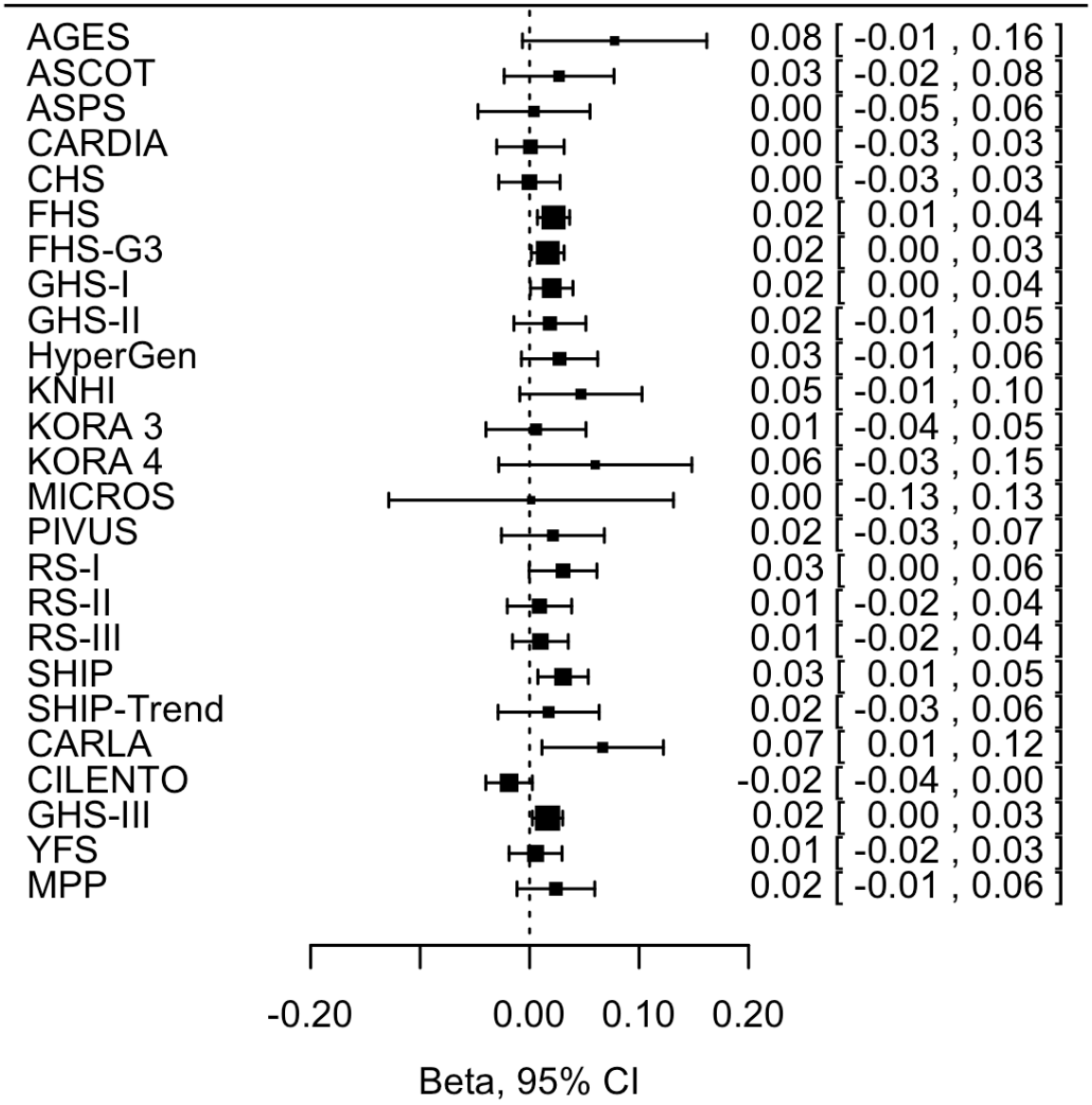
n=30,704

AoD rs17696696



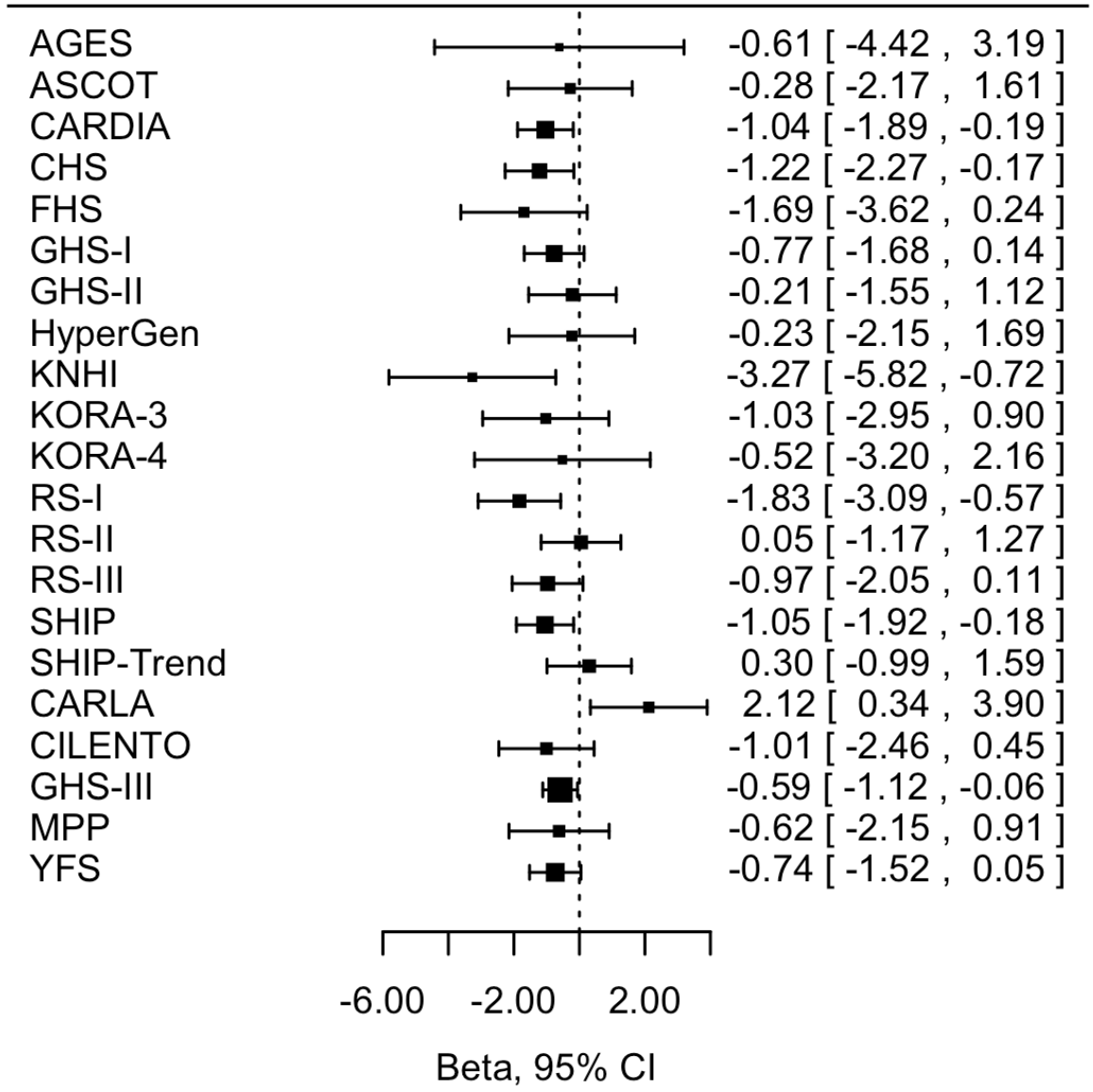
n=30,704

LVDD rs10774625



n=43,623

Mv-A rs12440869

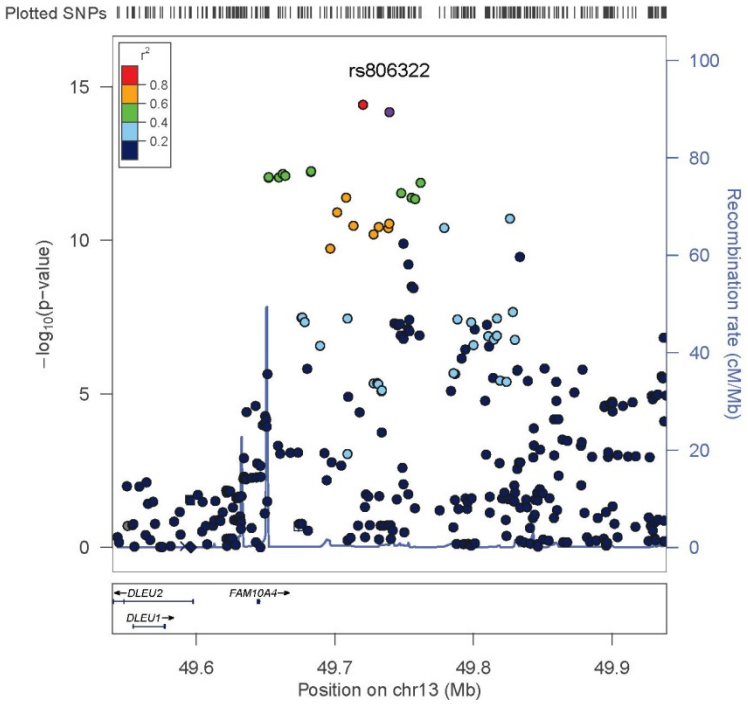


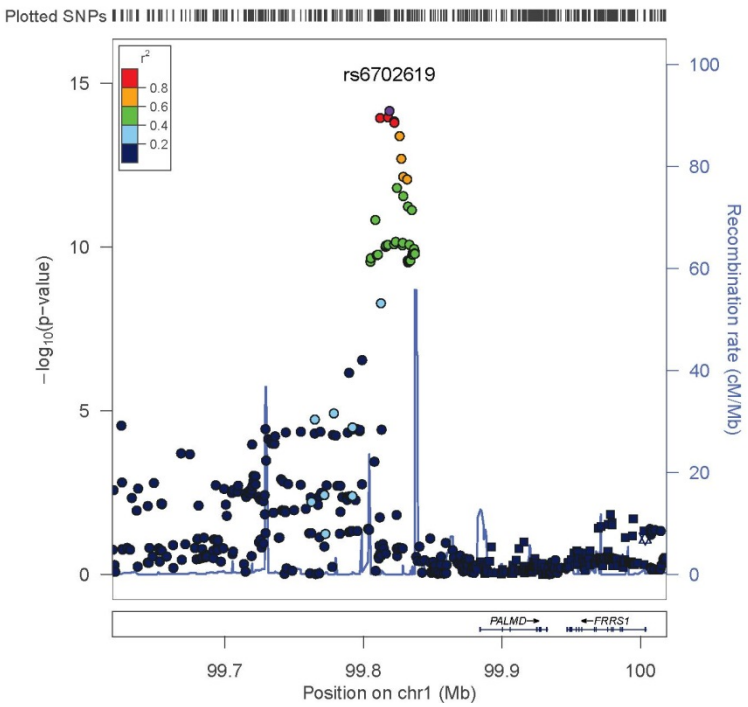
n=36,430

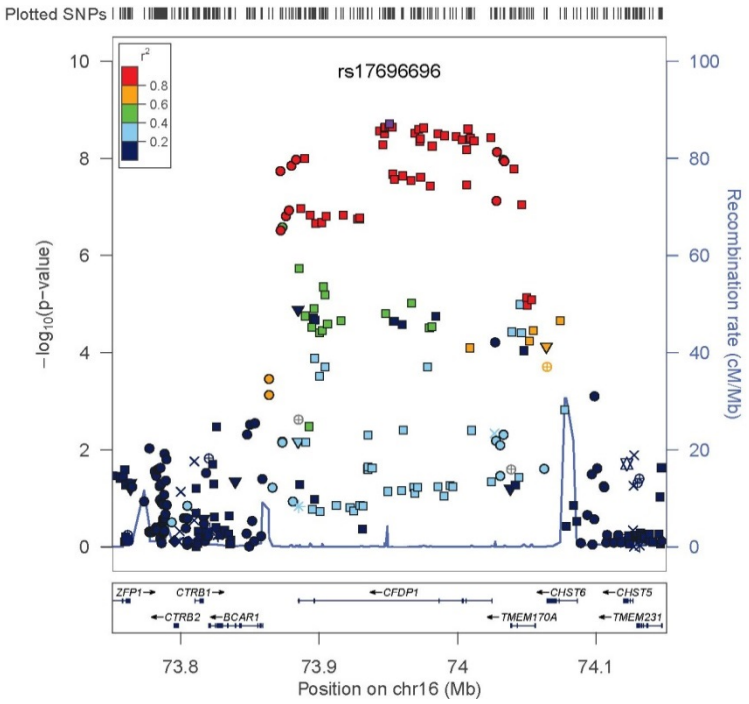
Figure S 18: Regional plots for all genome-wide significant hits.

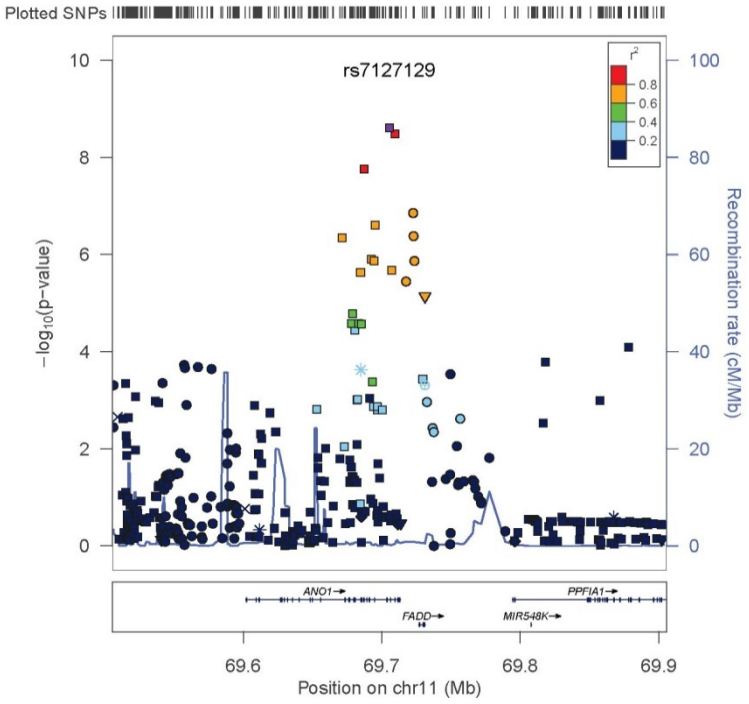
P values were obtained by calculating Wald test statistics

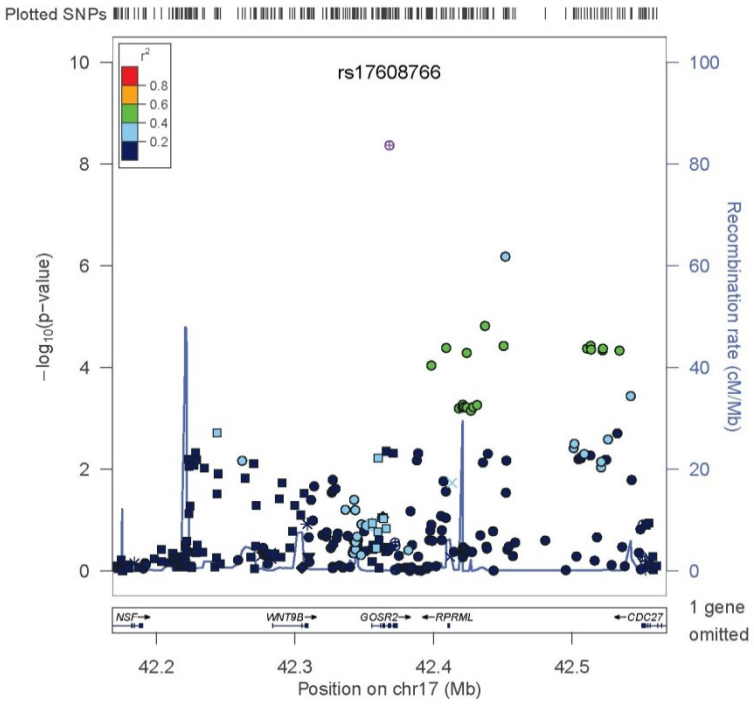
AoD, n=26,741

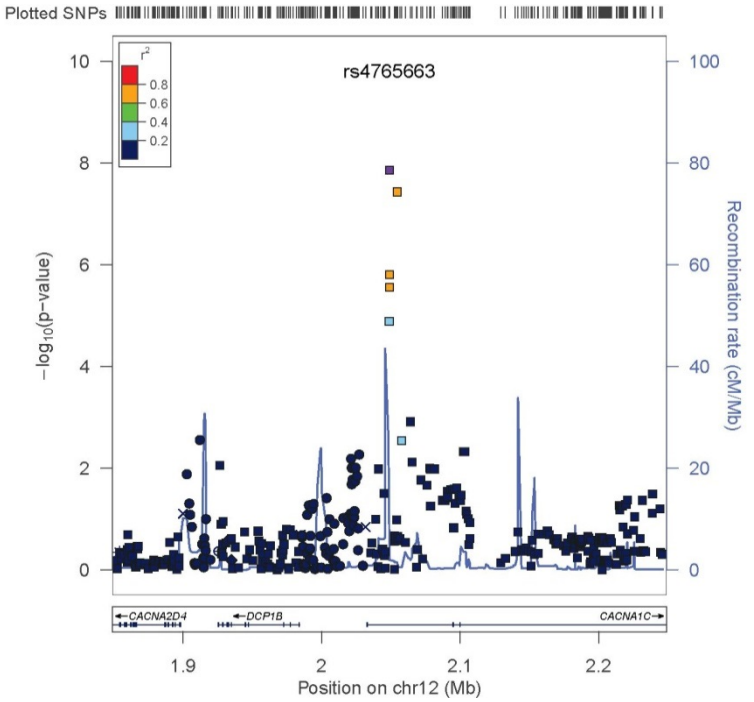


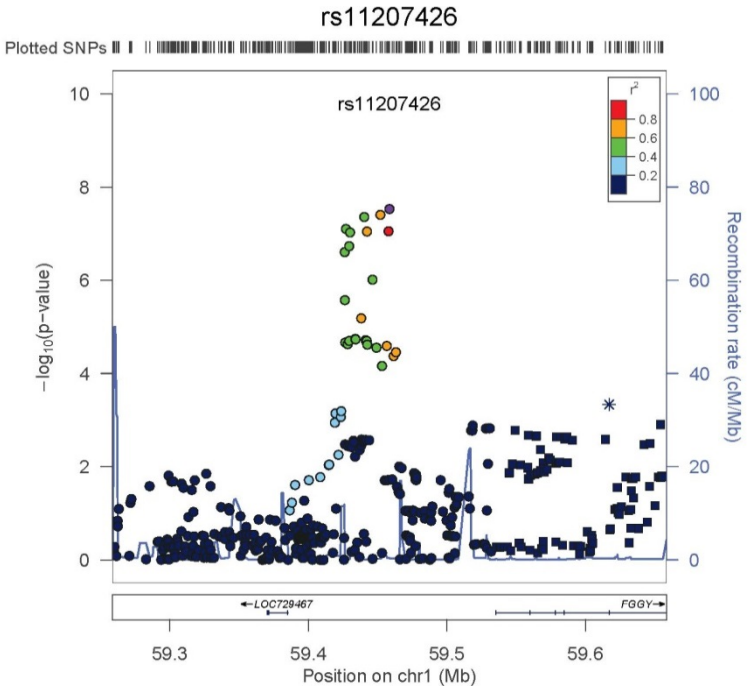



Plotted SNPs
rs17696696
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
ZFP1
CTRB1
CTRB2
BCAR1
CFDP1
CHST6
CHST5
TMEM170A
TMEM231
73.8
73.9
74
74.1
Position on chr16 (Mb)

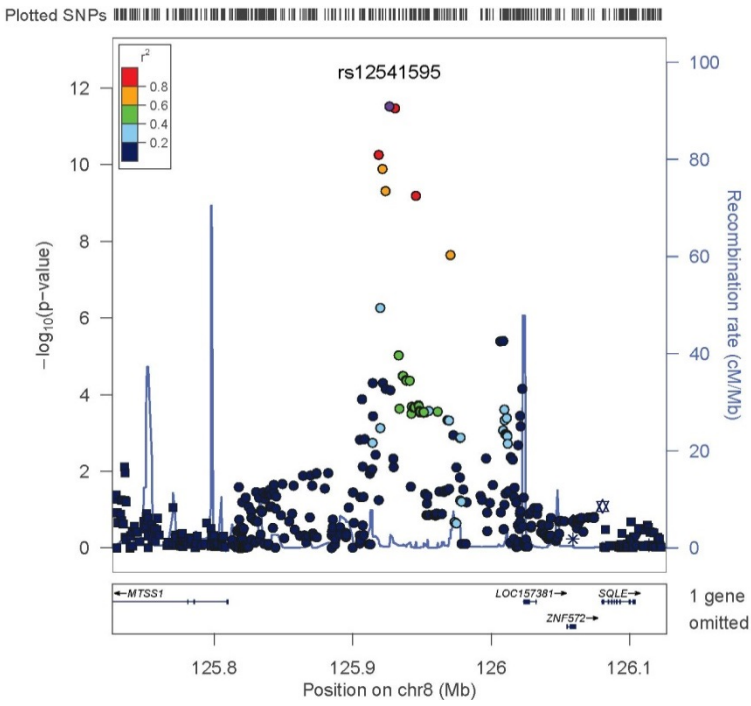

Plotted SNPs
rs7127129
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
ANO1
FADD
PPFIA1
MIR548K
69.6
69.7
69.8
69.9
Position on chr11 (Mb)

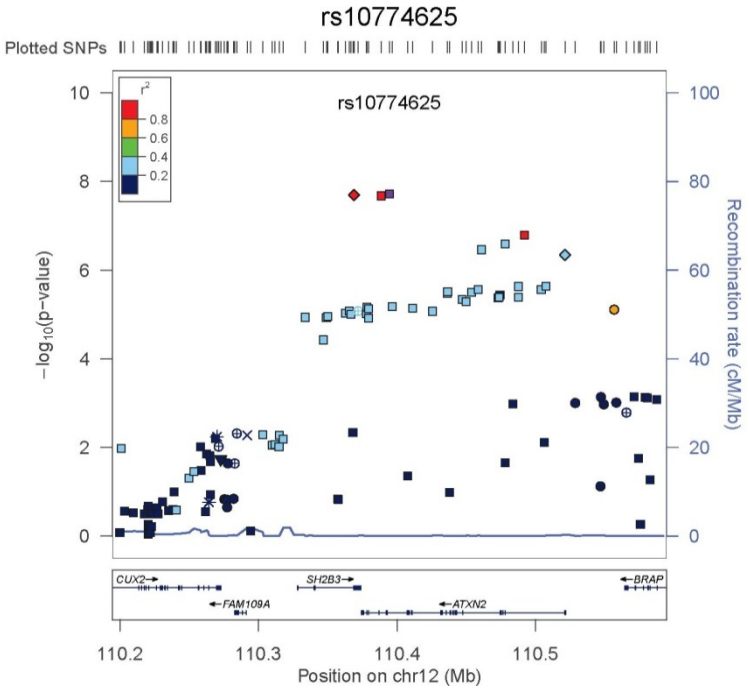

Plotted SNPs
rs17608766
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
NSF
WNT9B
GOSR2
RPRML
CDC27
1 gene omitted
Position on chr17 (Mb)


Plotted SNPs
rs4765663
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
CACNA2D4
DCP1B
CACNA1C
Position on chr12 (Mb)


rs11207426
Plotted SNPs
rs11207426
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
LOC729467
FGGY
59.3
59.4
59.5
59.6
Position on chr1 (Mb)

LVDD, n=30,201


Plotted SNPs
rs12541595
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
MTSS1
LOC157381
SQLE
ZNF572
1 gene omitted
125.8
125.9
126
126.1
Position on chr8 (Mb)


rs10774625
Plotted SNPs
rs10774625
r²
0.8
0.6
0.4
0.2
−log10(p-value)
Recombination rate (cM/Mb)
CUX2
SH2B3
BRAP
FAM109A
ATXN2
Position on chr12 (Mb)

Mv-A, n=21,643

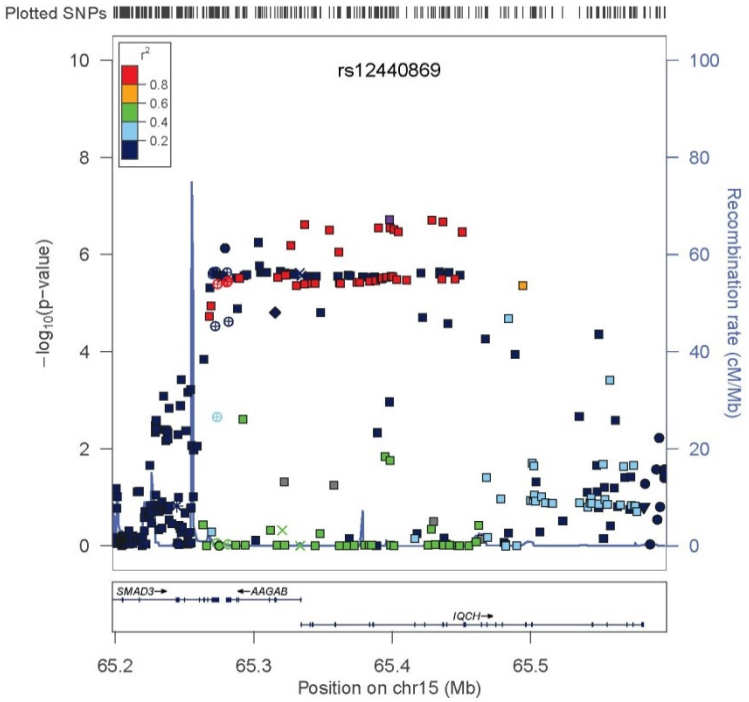
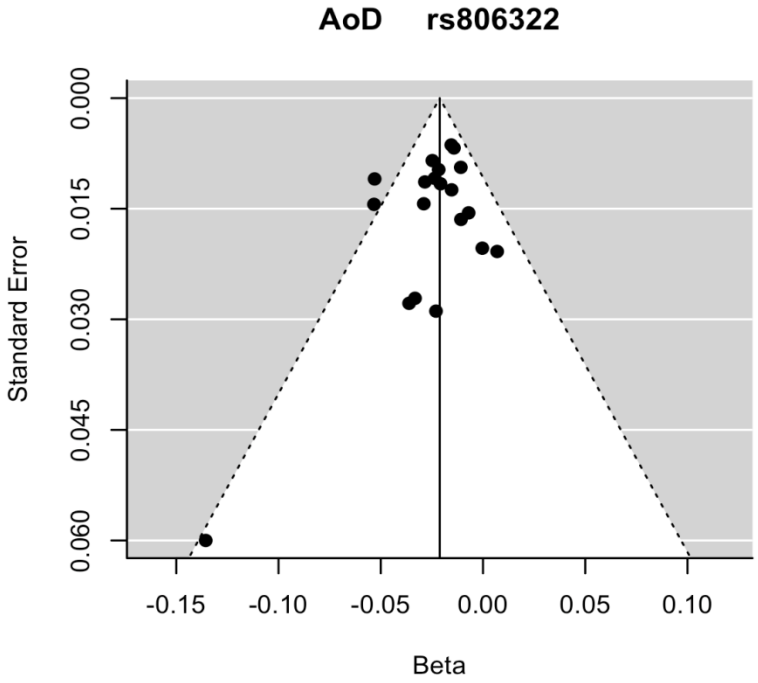
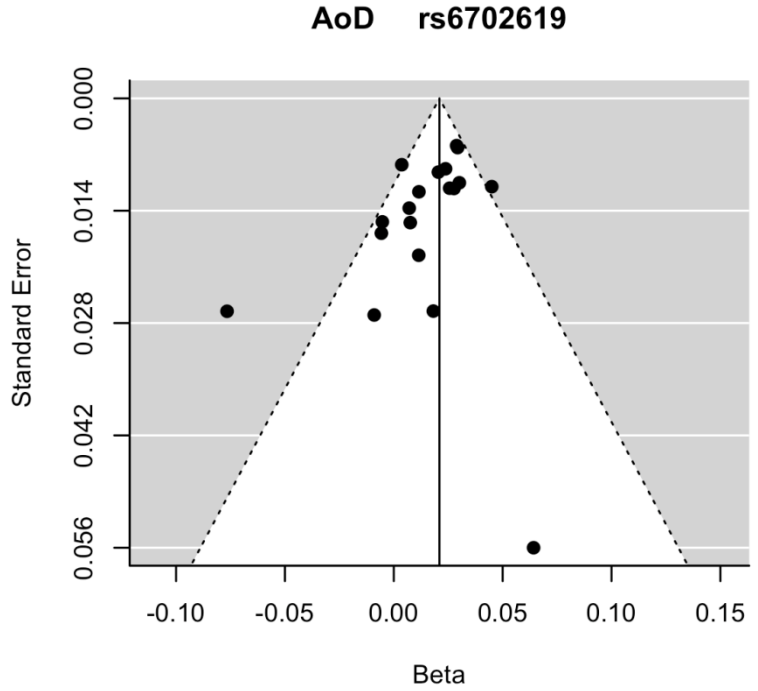
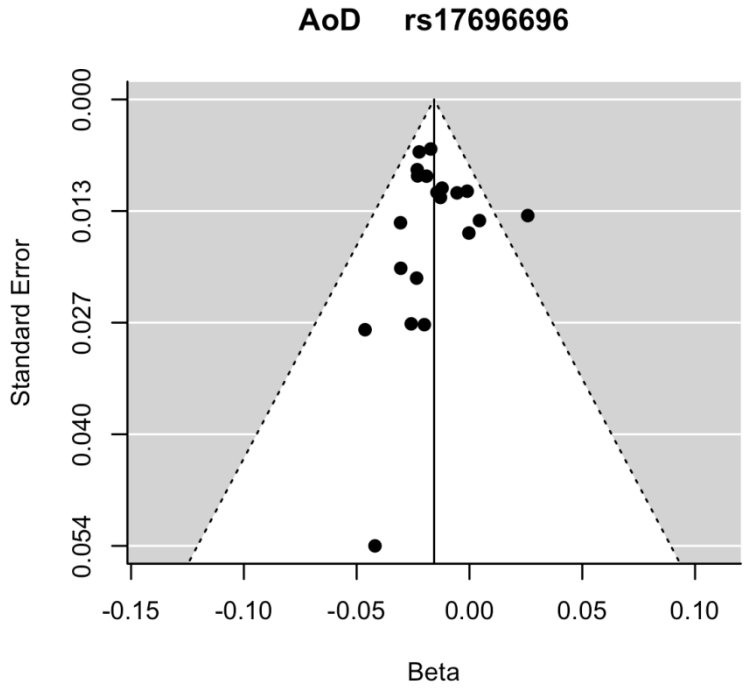
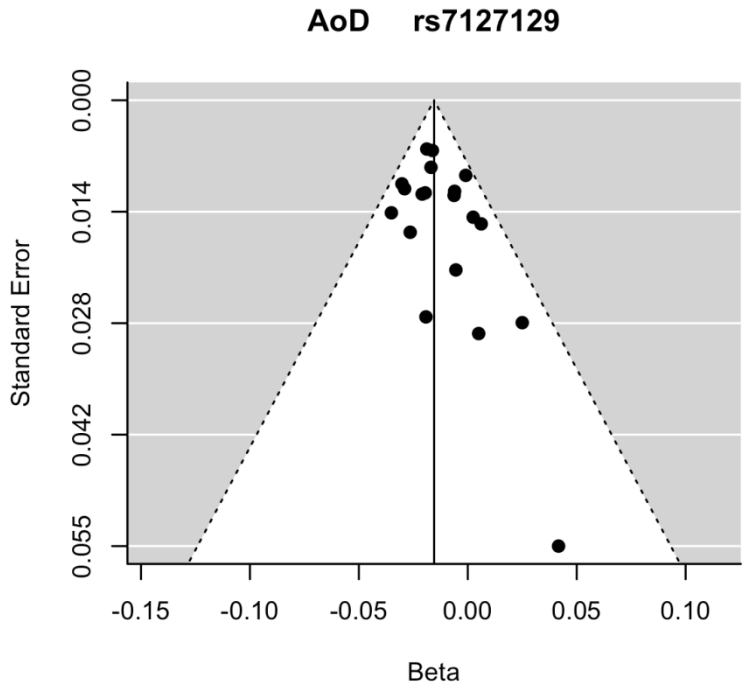

Plotted SNPs
rs12440869
r²
0.8
0.6
0.4
0.2
−log10(p-value)
Recombination rate (cM/Mb)
SMAD3
AAGAB
IQCH
Position on chr15 (Mb)

Figure S 19: Funnel plots for the novel genome-wide significant hits






AoD rs17696696
Standard Error
0.000
0.013
0.027
0.040
0.054
-0.15
-0.10
-0.05
0.00
0.05
0.10
Beta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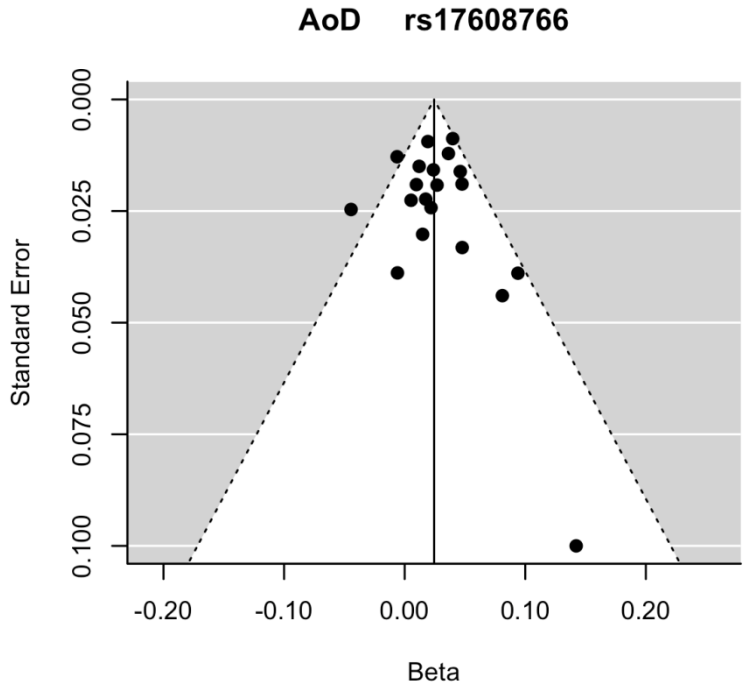
0.014
0.028
0.042
0.055
-0.15
-0.10
-0.05
0.00
0.05
0.10
Beta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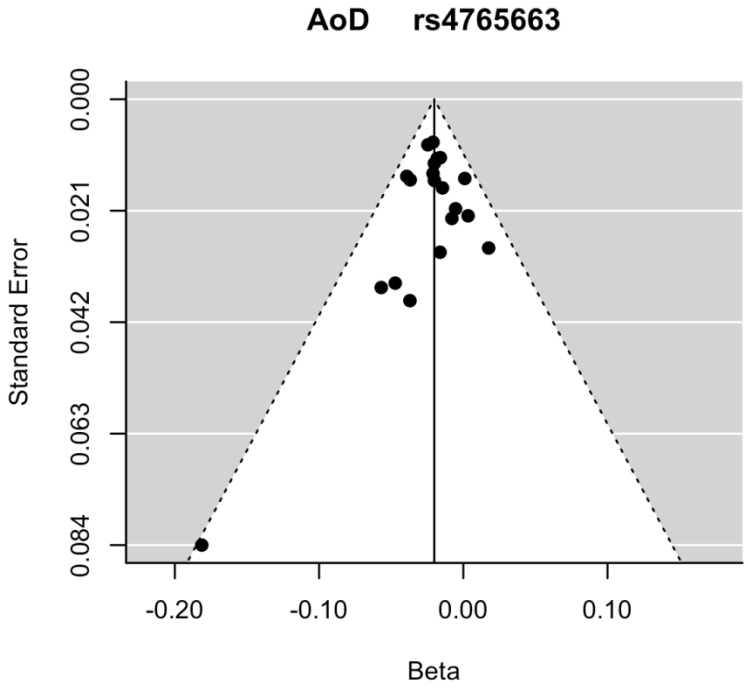
0.050
0.075
0.100
-0.20
-0.10
0.00
0.10
0.20
Beta


AoD rs4765663
Standard Error
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0.021
0.042
0.063
0.084
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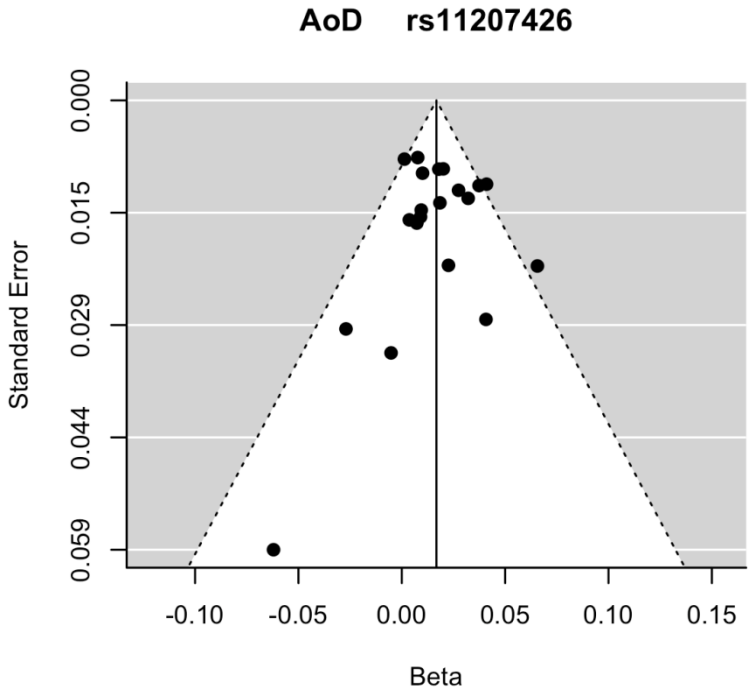
-0.10
0.00
0.10
Beta


AoD rs11207426
Standard Error
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0.015
0.029
0.044
0.059
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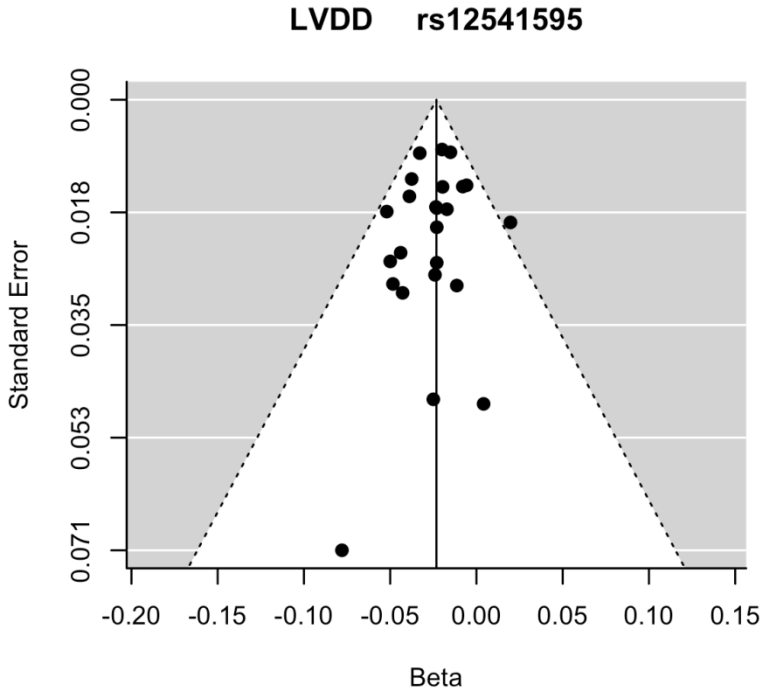
-0.05
0.00
0.05
0.10
0.15
Beta


LVDD rs12541595
Standard Error
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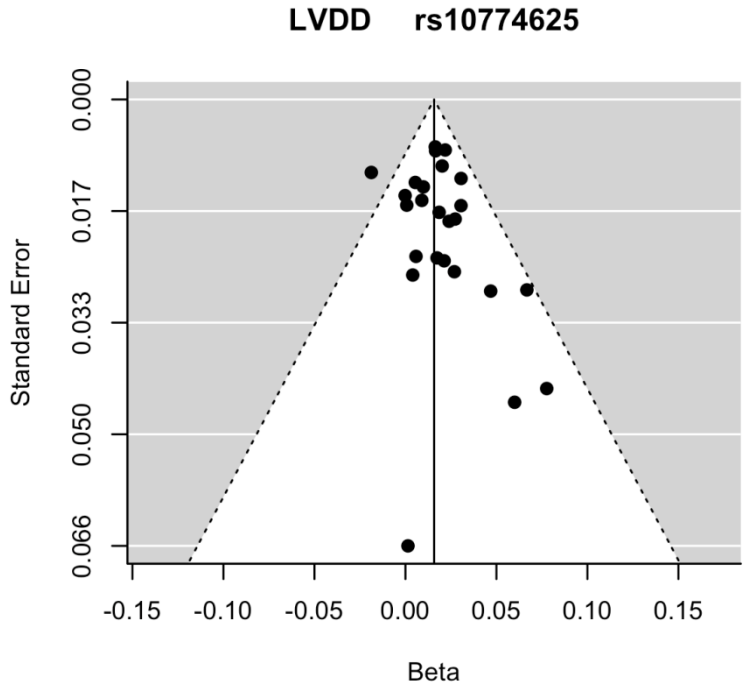
0.018
0.035
0.053
0.071
-0.20
-0.15
-0.10
-0.05
0.00
0.05
0.10
0.15
Beta


LVDD rs10774625
Standard Error
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0.033
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-0.10
-0.05
0.00
0.05
0.10
0.15
Beta

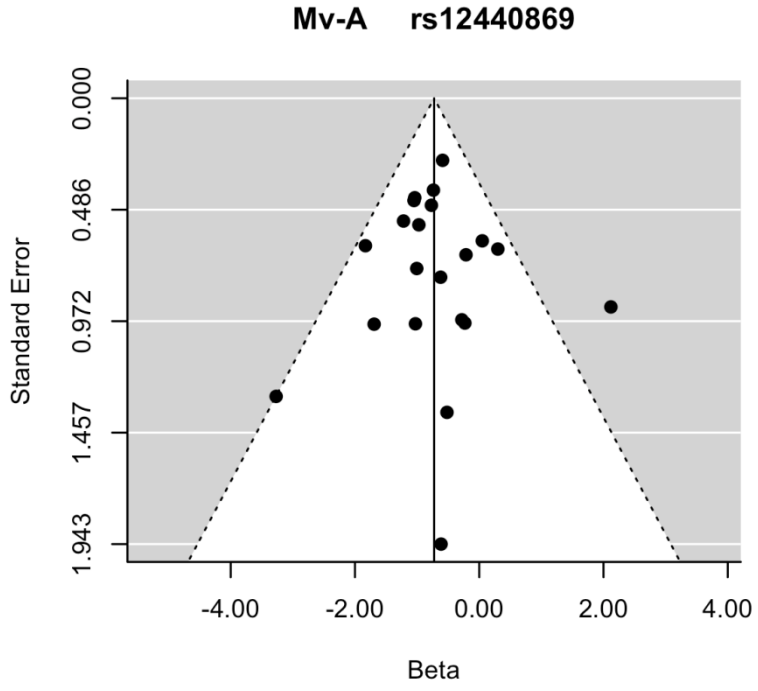
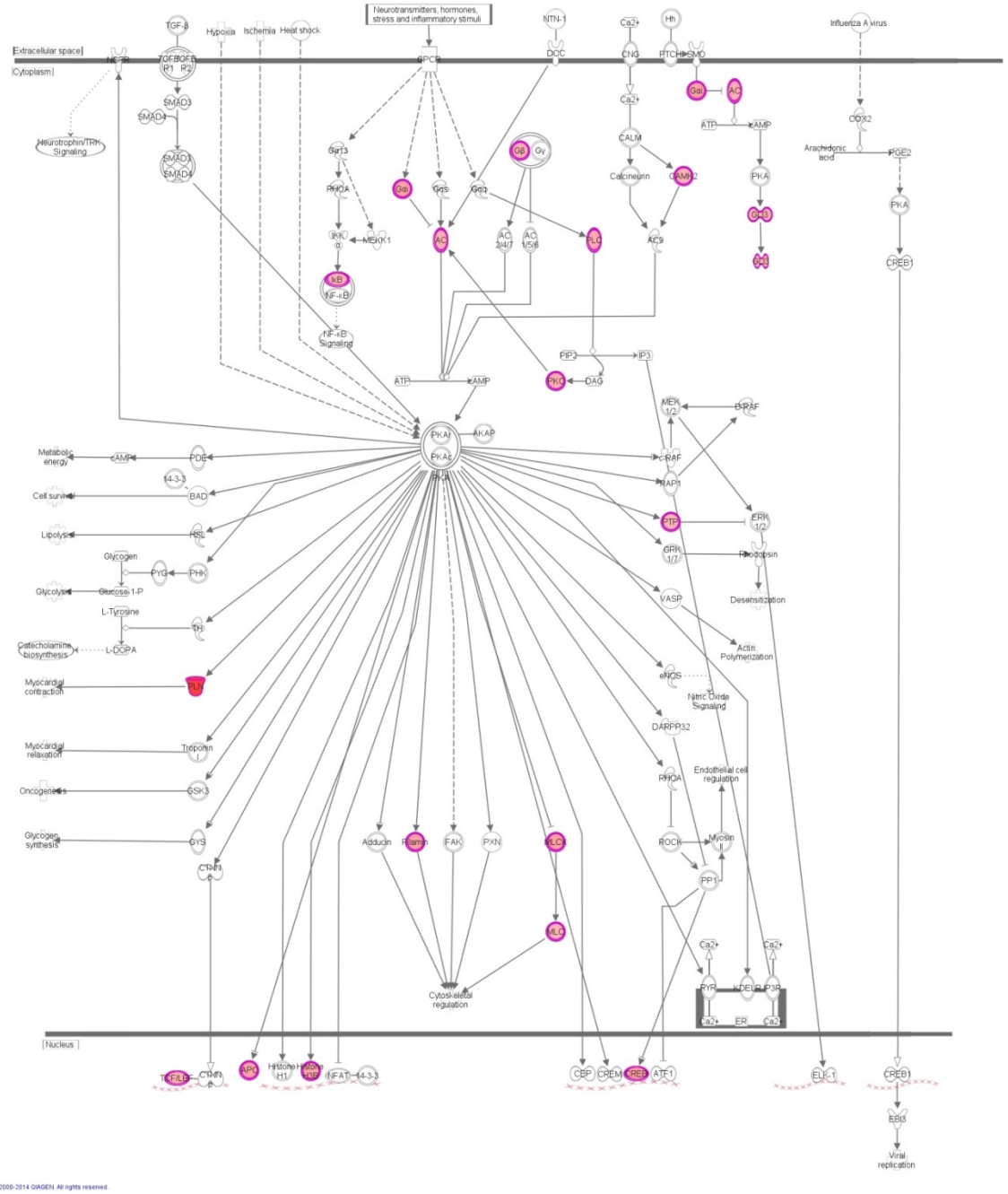

Mv-A rs12440869
Standard Error
0.000
0.486
0.972
1.457
1.943
-4.00
-2.00
0.00
2.00
4.00
Beta

Figure S 20: Protein Kinase A Signaling (pathway analysis)



Pathway analysis using Ingenuity IPA (Ingenuity Systems, Redwood, CA, USA). Red nodes are genes related to echo traits.

4 Acknowledgements

General funding and acknowledgements

This work was supported by a grant from the National Heart, Lung, and Blood Institute, USA (contract no: N01-HL-25195; R01HL 093328 to RSV), a MAIFOR grant from the University Medical Center Mainz, Germany (to PSW), the “Center for Translational Vascular Biology (CTVB)” of the Johannes Gutenberg-University of Mainz, and the Federal Ministry of Research and Education, Germany (contract no: BMBF 01EO1003 to PSW). This work was also supported by the research project Greifswald Approach to Individualized Medicine (GANI_MED). GANI_MED has been funded by the Federal Ministry of Education and Research and the Ministry of Cultural Affairs of the Federal State of Mecklenburg, West Pomerania (contract no: 03IS2061A).

We would like to thank all study participants, and the colleagues and coworkers from all cohorts and sites who were involved in the generation of data or in the analysis. We especially thank Andrew Johnson (Framingham Heart Study) for generation of the gene annotation database used for analysis. We thank the German Center for Cardiovascular Research (DZHK e.V.) for supporting the analysis and publication of this project. RSV is a member of the Scientific Advisory Board of the DZHK. Data on coronary artery disease and myocardial infarction have been contributed by CARDIoGRAMplusC4D investigators and have been downloaded from www.CARDIOGRAMPLUSC4D.ORG

Study-specific acknowledgements, funding and ethics statements

AortaGen Consortium

For full acknowledgements and funding information, please refer to Mitchell et al. (45).

Age, Gene/Environment Susceptibility (AGES) Study

The Age, Gene/Environment Susceptibility Study has been funded by NIH contract N01-AG-1-2100, the NIA Intramural Research Program, Hjartavernd (the Icelandic Heart Association), and the Althingi (the Icelandic Parliament). The study is approved by the Icelandic National Bioethics Committee, VSN: 00-063. The researchers are indebted to the participants for their willingness to participate in the study. The AGES Reykjavik Study GWAS was approved by the National Bioethics Committee (VSN: 00-063) and the Data Protection Authority. Informed consent was obtained from all participants.

Anglo-Scandinavian Cardiac Outcomes Trial - Hypertension Association Cardiovascular Disease (ASCOT) Study

The Anglo-Scandinavian Cardiac Outcomes Trial and the establishment of the associated genetic repository were funded by Pfizer, New York, USA with some additional funding provided by Servier Research Group, Paris, France, and Leo Laboratories, Copenhagen, Denmark. Genotyping was funded by Barts, the London School of Medicine and Dentistry, and by the Centre Nationale de Genotypage Paris. The research was also in part funded by an Irish Research Council GREP award. We thank the other investigators, the staff, and the participants of the ASCOT study for their important contributions. The study conformed to good clinical practice guidelines and was approved by the respective local hospital ethics committees (St. Mary's Hospital, London, UK and Beaumont Hospital, Dublin, Ireland). Written informed consent for the study was obtained from all participants.

Austrian Stroke Prevention Study (ASPS)

Current analyses of ASPS are funded by the Austrian Science Fund Project P20545_P05 Genetics of cerebral small vessel disease (to H Schmidt). We are indebted to Birgit Reinhart for her continuous administrative support in the setting of the Austrian Stroke Prevention Study and to Johann Semmler for his high-quality technical assistance. The authors thank the staff and the participants of the ASPS for their valuable contributions. The study protocol was approved and accepted by the ethics committee of the Medical University of Graz, Austria, and informed consent was obtained from all study participants.

Coronary Artery Risk Development in Young Adults (CARDIA) Study

The CARDIA Study is conducted and supported by the National Heart, Lung, and Blood Institute in collaboration with the University of Alabama at Birmingham (HHSN268201300025C & HHSN268201300026C), Northwestern University (HHSN268201300027C), University of Minnesota (HHSN268201300028C), Kaiser Foundation Research Institute (HHSN268201300029C), and Johns Hopkins University School of Medicine (HHSN268200900041C). CARDIA is also partially supported by the Intramural Research Program of the National Institute on Aging. Genotyping and imputation were funded as part of the Gene Environment Association Studies (GENEVA) through grants U01-HG004729, U01-HG04424, and U01-HG004446 from the National Human Genome Research Institute. This manuscript has been reviewed and approved by CARDIA for scientific content. SJ Shah is supported by R01 HL1075755. Informed consent was obtained from all participants, and the institutional review board at each participating CARDIA center approved the study.

Cardiovascular Disease, Living and Ageing in Halle (CARLA) Study

This study was funded by a grant from the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) as part of the Collaborative Research Center 598 ‘‘Heart failure in the elderly–cellular mechanisms and therapy’’ at the Medical Faculty of the Martin-Luther-University Halle-Wittenberg; by a grant of the Wilhelm-Roux Programme of the Martin-Luther-University Halle-Wittenberg; by the Federal Employment Office; and by the Ministry of Education and Cultural Affairs of Saxony-Anhalt. The study was in accordance with the declaration of Helsinki. All participants gave their written informed consent. The study was approved by the local ethic commission of the Medical Faculty of the Martin-Luther-University Halle-Wittenberg.

Cohorts for Heart and Aging Research in Genomic Epidemiology– Heart Failure Working Group (CHARGE-HF)

For a full list of CHARGE-HF working group members contributing to this work and for CHARGE-HF acknowledgements, please reference (3).

Cardiovascular Health Study (CHS)

Cardiovascular Health Study: This CHS research was supported by NHLBI contracts HHSN268201200036C, HHSN268200800007C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086, N01HC85084, N01HC35129; and NHLBI grants U01HL080295, R01HL087652, R01HL105756, R01HL103612, and R01HL120393 with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided through R01AG023629 from the National Institute on Aging (NIA). A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org. The provision of genotyping data was supported in part by the National Center for Advancing

Translational Sciences, CTSI grant UL1TR000124, and the National Institute of Diabetes and Digestive and Kidney Disease Diabetes Research Center (DRC) grant DK063491 to the Southern California Diabetes Endocrinology Research Center. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. CHS was approved by institutional review committees at each site, the subjects gave informed consent, and those included in the present analysis consented to the use of their genetic information for the study of cardiovascular disease.

Genetic Park of Cilento and Vallo di Diano Project **(Cilento)**

This work was supported by grants from the Italian Ministry of Universities and CNR (Interomics Flagship Project, PON03PE_00060_7), the Assessorato Ricerca Regione Campania, the Fondazione con il SUD (2011-PDR-13), and the Istituto Banco di Napoli - Fondazione to MC. We thank the populations of Cilento for their participation in the study.

We thank Dr. Gianluigi Iovino for echocardiographic examinations. The study design was approved by the ethics committee of Azienda Sanitaria Locale Napoli 1. The study was conducted according to the criteria set by the declaration of Helsinki and each subject signed an informed consent before participating to the study.

DEPICT

TH Pers is supported by The Danish Council for Independent Research Medical Sciences (FSS) and The Alfred Benzon Foundation.

Framingham Heart Study, original cohort, offspring and third generation (FHS1, FHS2, FHS3)

This work was partially supported by the National Heart, Lung and Blood Institute's Framingham Heart Study (Contracts No. N01-HC-25195 and HHSN268201500001I), research grants (5R01HL107385-04 1R01HL126136-01A1), and a contract with Affymetrix, Inc for genotyping services (Contract No. N02-HL-6-4278). A portion of this research utilized the Linux Cluster for Genetic Analysis (LinGA-II) funded by the Robert Dawson Evans Endowment of the Department of Medicine at Boston University School of Medicine and Boston Medical Center. This research was conducted in part using data and resources from the Framingham Heart Study of the National Heart Lung and Blood Institute of the National Institutes of Health and Boston University School of Medicine. The analyses reflect intellectual input and resource development from the Framingham Heart Study investigators participating in the SNP Health Association Resource (SHARe) project. Each study participant provided written informed consent for participation in the study and for genetic analyses and the study was approved by the Boston University Medical Center Institutional Review Board.

The Generation R Study (Generation R)

The general design of Generation R Study is made possible by financial support from the Erasmus Medical Center, Rotterdam, the Erasmus University Rotterdam, the Netherlands Organization for Health Research and Development (ZonMw), the Netherlands Organisation for Scientific Research (NWO), the Ministry of Health, Welfare and Sport and the Ministry of Youth and Families. VW Jaddoe received an additional grant from the Netherlands Organization for Health Research and Development (VIDI 016.136.361) and a European Research Council Consolidator Grant (ERC-2014-CoG-648916). The Generation R Study is conducted by the Erasmus Medical Center in close

collaboration with the School of Law and Faculty of Social Sciences of the Erasmus University Rotterdam, the Municipal Health Service Rotterdam area, Rotterdam, the Rotterdam Homecare Foundation, Rotterdam and the Stichting Trombosedienst & Artsenlaboratorium Rijnmond (STAR-MDC), Rotterdam. We gratefully acknowledge the contribution of children and parents, general practitioners, hospitals, midwives and pharmacies in Rotterdam. The generation and management of GWAS genotype data for the Generation R Study were done at the Genetic Laboratory of the Department of Internal Medicine, Erasmus MC, the Netherlands. We would like to thank Karol Estrada, Dr. Tobias A. Knoch, Anis Abuseiris, Luc V. de Zeeuw, and Rob de Graaf, for their help in creating GRIMP, BigGRID, MediGRID, and Services@MediGRID/D-Grid, (funded by the German Bundesministerium fuer Forschung und Technology; grants 01 AK 803 A-H, 01 IG 07015 G) for access to their grid computing resources. We thank Mila Jhamai, Manoushka Ganesh, Pascal Arp, Marijn Verkerk, Lizbeth Herrera and Marjolein Peters for their help in creating, managing and QC of the GWAS database. Also, we thank Karol Estrada for his support in creation and analysis of imputed data. The Generation R Study is made possible by financial support from the Erasmus Medical Center, Rotterdam, the Erasmus University Rotterdam and the Netherlands Organization for Health Research and Development. The study protocol was approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam. Written informed consent was obtained for all participants.

Gutenberg Health Study (GHS-I, -II, -III)

The Gutenberg Health Study is funded through the government of Rhineland-Palatinate („Stiftung Rheinland-Pfalz für Innovation“, contract AZ 961-386261/733), the research

programs “Wissen schafft Zukunft” and “Center for Translational Vascular Biology (CTVB)” of the Johannes Gutenberg-University of Mainz, and its contract with Boehringer Ingelheim and PHILIPS Medical Systems, including an unrestricted grant for the Gutenberg Health Study. PS Wild is funded by the Federal Ministry of Education and Research (BMBF 01EO1003) and he received honoraria for lectures or consulting from Boehringer Ingelheim and Bayer HealthCare, Leverkusen. We thank all study participants for their willingness to provide data for this research project and we are indebted to all coworkers for their enthusiastic commitment. The study followed the recommendations of the Declaration of Helsinki and was approved by the ethics committee of the Chamber of Physicians of Rhineland-Palatinate, Germany (reference no. 837.020.07). Written informed consent was obtained from all participants.

Hypertension Genetic Epidemiology Network (HyperGEN)

The HyperGEN Echocardiography ancillary study was funded by the National Institutes of Health (R01 HL 55673). The HyperGEN parent study was funded by cooperative agreements (U10) with the National Heart, Lung, and Blood Institute: HL54471, HL54472, HL54473, HL54495, HL54496, HL54497, HL54509, HL54515. The authors thank the HyperGEN participants and staff for their valuable contributions. HyperGEN was approved by the institutional review committees at each site. All participants gave informed consent, and those included in the present analysis consented to the use of their genetic information for cardiovascular disease or related conditions.

Jackson Heart Study (JHS)

The Jackson Heart Study is supported by contracts HSN268201300046C, HHSN268201300047C, HHSN268201300048C, HHSN268201300049C,

HHSN268201300050C from the National Heart, Lung, and Blood Institute on Minority Health and Health Disparities. The authors thank the Jackson Heart Study team (University of Mississippi Medical Center, Jackson State University and Tougaloo College) and participants for their long-term commitment that continues to improve our understanding of the genetic epidemiology of cardiovascular and other chronic diseases. The study protocol was approved by the University of Mississippi Medical Center Internal Review Board committee on human subjects. All participants gave informed consent.

Kompetenznetz Herzinsuffizienz (KNHI)

EB, BP, HB and GH received funding by the national genome research network NGFN of the BMBF (grant numbers 01GS0837 and 01GS0422, funding MS and DMalzahn); FE and BP received funding by the competence network heart failure Germany. The study was approved by the ethics committee of the Georg-August-University in Göttingen, Germany and all participants gave informed consent.

Cooperative Health Research in the Region of Augsburg, followup studies F3 and F4 (KORA-F3 and –F4)

The Cooperative Health Research in the Region of Augsburg studies were financed by the Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany and supported by grants from the German Federal Ministry of Education and Research (BMBF). Part of this work was financed by the German National Genome Research Network (NGFN). Our research was supported within the Munich Center of Health Sciences (MC Health) as part of LMUinnovativ. The studies

were approved by the local ethics committees and all participants gave informed consent.

Ludwigshafen Risk and Cardiovascular Health (LURIC) Study

This work was supported by the 7th Framework Program (AtheroRemo, grant agreement number 201668 and RiskyCAD, grant agreement number 305739) of the EU and by the INTERREG-IV-Oberrhein-Program (Project A28, Genetic mechanisms of cardiovascular diseases) with support from the European Regional Development Fund (ERDF) and the Wissenschaftsoffensive TMO. We extend our appreciation to the participants of the LURIC study and thank the LURIC study team who were either temporarily or permanently involved in patient recruitment as well as sample and data handling, in addition to the laboratory staff at the Ludwigshafen General Hospital and the Universities of Freiburg and Ulm, Germany. The study was approved by the ethics committee at the "Landesärztekammer Rheinland-Pfalz" and was conducted in accordance with the "Declaration of Helsinki". Informed written consent was obtained from all participants.

Myocardial Applied Genomics Network (MAGNet)

MAGNet (http://www.med.upenn.edu/magnet/) is funded by NIH R01HL105993. MAGNet protocols have been approved by institutional review boards at University of Pennsylvania, Stanford University, and Cleveland Clinic, Gift of Life.

Microisolates in South Tyrol (MICROS) Study

The MICROS study was supported by the Ministry of Health and Department of Educational Assistance, University and Research of the Autonomous Province of Bolzano, the South Tyrolean Sparkasse Foundation, and the European Union

framework program 6 EUROSPAN project (contract no. LSHG-CT-2006-018947). For the MICROS study, we thank the primary care practitioners Raffaela Stocker, Stefan Waldner, Toni Pizzecco, Josef Plangger and Ugo Marcadent, and Helmuth Weiss and the personnel of the Hospital of Silandro (Department of Laboratory Medicine) for their participation and collaboration in the research project. The MICROS study was approved by the ethical committee of the Autonomous Province of Bolzano. Informed consent was obtained from all participants.

Malmö Preventive Project (MPP)

This work in the MPP was supported by grants from the the Swedish Heart-Lung Foundation (JGS, OM, PN), the Swedish Research Council (to JGS and OM), the European Research Council (OM), the Faculty of Medicine of Lund University (OM), Skåne University Hospital (JGS, OM) and the Crafoord Foundation (JGS, OM). This study was approved by the Ethics Committee of Lund University. All participants provided written informed consent before entering the study.

Northern Manhattan Study (NOMAS)

NOMAS is supported by the National Institute of Neurological Disorders and Stroke (NINDS) of the National Institutes of Health (NIH) through grants R37 NS2993 (Dr. Sacco and Elkind) and R01 NS36286 (Dr. Di Tullio). MDT is supported by grant NINDS R01 NS083784. RLS and NDD are supported by McKnight Brain Foundation. The authors gratefully acknowledge Ashley Beecham and Shengru Guo for their analytical support. The authors also gratefully acknowledge the McKnight Institute for providing funding to genotype NOMAS participants. All patients provided informed consent to

participate in the study. The study was approved by the Institutional Review Boards of Columbia University and the University of Miami.

Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) Study

This study was supported by grants from the Swedish Foundation for Strategic Research (project grant no. ICA08-0047), the Swedish Research Council (project grant no. 2012-1397), the Swedish Heart-Lung Foundation (project grant no. 20120197), the Swedish Society of Medicine, and Uppsala University. Genotyping was performed by the SNP&SEQ Technology Platform in Uppsala (www.genotyping.se), which is supported by Uppsala University, Uppsala University Hospital, Science for Life Laboratory - Uppsala and the Swedish Research Council (Contracts 80576801 and 70374401). Genotyping was performed by the SNP&SEQ Technology Platform in Uppsala (www.genotyping.se). We thank Tomas Axelsson, Ann-Christine Wiman and Caisa Pöntinen for their excellent assistance with genotyping. APM is a Wellcome Trust Senior Research Fellow in Basic Biomedical Science (grant number WT098017). The study was approved by the Ethics Committee of Uppsala University and all participants provided informed consent.

Rotterdam Study (RS)-I, -II, -III

The generation and management of GWAS genotype data for the Rotterdam Study is supported by the Netherlands Organisation of Scientific Research NWO Investments (nr. 175.010.2005.011, 911-03-012). This study is funded by the Research Institute for Diseases in the Elderly (014-93-015; RIDE2), the Netherlands Genomics Initiative (NGI)/Netherlands Organisation for Scientific Research (NWO) project nr. 050-060-810. The Rotterdam Study is funded by Erasmus Medical Center and Erasmus University,

Rotterdam, Netherlands Organization for the Health Research and Development (ZonMw), the Research Institute for Diseases in the Elderly (RIDE), the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the European Commission (DG XII), and the Municipality of Rotterdam. OH Franco works in ErasmusAGE, a center for aging research across the life course funded by Nestlé Nutrition (Nestec Ltd.), Metagenics Inc. and AXA. Nestlé Nutrition (Nestec Ltd.), Metagenics Inc. and AXA had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review or approval of the manuscript. The generation and management of GWAS genotype data for the Rotterdam Study is supported by the Netherlands Organisation of Scientific Research NWO Investments (nr. 175.010.2005.011, 911-03-012). This study is funded by the Research Institute for Diseases in the Elderly (014-93-015; RIDE2), the Netherlands Genomics Initiative (NGI)/Netherlands Organisation for Scientific Research (NWO) project nr. 050-060-810. We thank Pascal Arp, Mila Jhamai, Marijn Verkerk, Lizbeth Herrera and Marjolein Peters for their help in creating the GWAS database, and Karol Estrada and Maksim V. Struchalin for their support in creation and analysis of imputed data. The Rotterdam Study is funded by Erasmus Medical Center and Erasmus University, Rotterdam, Netherlands Organization for the Health Research and Development (ZonMw), the Research Institute for Diseases in the Elderly (RIDE), the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the European Commission (DG XII), and the Municipality of Rotterdam. The authors are grateful to the study participants, the staff of the Rotterdam Study and the participating general practitioners and pharmacists. The Rotterdam Study has been approved by the

Medical Ethics Committee of the Erasmus MC and by the Dutch Ministry of Health, Welfare and Sport, implementing the “Wet Bevolkings Onderzoek: ERGO (Population Screening Act: Rotterdam Study). All participants provided written informed consent to participate in the study and to obtain information from their treating physicians.

Study of Health in Pomerania (SHIP and SHIP-Trend)

SHIP is part of the Community Medicine Research net of the University of Greifswald, Germany, which is funded by the Federal Ministry of Education and Research (grants no. 01ZZ9603, 01ZZ0103, and 01ZZ0403), the Ministry of Cultural Affairs as well as the Social Ministry of the Federal State of Mecklenburg-West Pomerania. Echocardiography in the 5-year follow-up (SHIP-1) was funded by the Competence Network Heart Failure of the Federal Ministry of Education and Research. Genome-wide data have been supported by the Federal Ministry of Education and Research (grant no. 03ZIK012) and a joint grant from Siemens Healthcare, Erlangen, Germany and the Federal State of Mecklenburg- West Pomerania. The University of Greifswald is a member of the Caché Campus program of the InterSystems GmbH. All participants gave informed written consent. The study followed the recommendations of the Declaration of Helsinki and was approved by the Ethics Committee of the University of Greifswald.

Uppsala Longitudinal Study of Adult Men (ULSAM)

This study was supported by grants from the Swedish Foundation for Strategic Research (project grant no. ICA08-0047), the Swedish Research Council (project grant no. 2012-1397), the Swedish Heart-Lung Foundation (project grant no. 20120197), the Swedish Society of Medicine, and Uppsala University. Genotyping was performed by the SNP&SEQ Technology Platform in Uppsala (www.genotyping.se), which is

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Role of the sponsors

The sponsors had no role in the study design, analyses, drafting of the manuscript, or the decision to publish.

Drs.Wild, Felix, Schillert, Teumer, Zeller, Vasan and Dörr had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.